CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-272

ADMINISTRATIVE DOCUMENTS

Time Sensitive Patent Information

Pursuant to 21 C.F.R. 314.53

for

NDA #21-272

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

- Trade Name: Uniprost™
- Active Ingredient(s): treprostinol sodium (Applied for)
- Strength(s): 1.0 mg/mL, 2.5 mg/mL, 5.0 mg/mL, 10.0 mg/mL
- Dosage Form: Injection
- Approval Date: NDA submitted October 16, 2000

A. This information should be provided for each individual patent submitted.

U.S. Patent Number: 5,153,222

Expiration Date: October 6, 2009

Type of Patent--Indicate all that apply:

1. Drug Substance (Active Ingredient) ___Y ✓N
2. Drug Product (Composition/Formulation) ___Y ✓N
3. Method of Use ✓Y ___N

a. If patent claims method(s) of use, please specify approved method(s)of use or method(s) of use for which approval is being sought that are covered by patent: Treatment of pulmonary hypertension with UT-15.

Name of Patent Owner: United Therapeutics Corp.

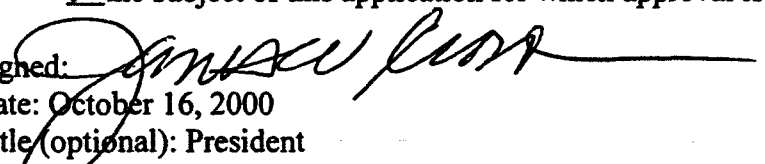
U.S. Agent (if patent owner or applicant does not reside or have place of business in the US): Not Applicable

The undersigned declares that the above stated United States Patent Number 5,153,222 covers the composition, formulation and/or method of use of Uniprost. This product is:

- ___currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act)

OR

- ✓ the subject of this application for which approval is being sought.)

Signed: 
Date: October 16, 2000
Title (optional): President
Telephone Number (optional): 919-485-8350

EXCLUSIVITY SUMMARY FOR NDA # 21-272 SUPPL #_____

Trade Name: Remodulin Generic Name: Treprostinil Sodium Injection

Applicant Name: United Therapeutics Co. HFD # 110

Approval Date If Known:

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES /_X__/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /_X__/

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /_X__/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES /___/ NO /_X__/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

NO

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /___/ NO /_X__/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II ~~FIVE~~SEVEN-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(NOTE: Remodulin (treprostinol) has been granted an orphan designation for pulmonary arterial hypertension)
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /_X__/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /_X__/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or

other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /___/ NO /___/ Explain: _____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

Signature Date
Title:

Signature of Office/ Date
Division Director

cc: Original NDA Division File HFD-93 Mary Ann Holovac

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

/s/

Raymond Lipicky
1/24/02 10:17:36 AM

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

DA/BLA # : NDA 21-272 **Supplement Type (e.g. SE5):** _____ **Supplement Number:** _____

Stamp Date: August 09, 2001 (resubmission) **Action Date:** February 9, 2002

HFD-110 **Trade and generic names/dosage form:** Remodulin (treprostinil sodium) Injection

Applicant: United Therapeutics Co. **Therapeutic Class:** 1PV (orphan)

Indication(s) previously approved: none

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Pulmonary Arterial Hypertension (PAH)

Is there a full waiver for this indication (check one)?

X **Yes: Please proceed to Section A.**

☐ **No: Please check all that apply:** ____Partial Waiver ____Deferred ____Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

ction A: Fully Waived Studies

Reason(s) for full waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
X **Other:** United Therapeutics requested a waiver from pediatric use information, in accordance with 21 CRF 314.55 (d). The requirement for pediatric use information has been waived because the drug has been granted orphan status.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for partial waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Adult studies ready for approval**

☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

/S/ 1-29-02

Regulatory Project Manager

cc: NDA
HFD-960/ Terrie Crescenzi
(revised 1-18-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
United Therapeutics Inc.	April 12, 2001
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE (FAX) Number** *(Include Area Code)* 919-485-8352
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* 68 T.W. Alexander Drive, Research Triangle Park, North Carolina 27709	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE: N/A

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 21-272

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
treprostinol sodium (applied for)	Remodulin

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*

CODE NAME *(If any)* UT-15

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Injection	1.0, 2.5, 5.0, 10.0 mg/mL	subcutaneous injection

(PROPOSED) INDICATION(S) FOR USE: Pulmonary Arterial Hypertension

APPLICATION INFORMATION

APPLICATION TYPE *(check one)* ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: *(Check all that apply)*

☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (k)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
[signature]	Dean Bunce, Director Regulatory Affairs	April 12, 2001

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
68 T.W. Alexander Drive, Research Triangle Park, N.C. 27709	(919) 485-8350

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Dr., Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

(1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	See Attached	

(2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

(3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
James Crow, Ph.D.	President
FIRM/ORGANIZATION: United Therapeutics Corp, 68 T.W. Alexander Drive, Research Triangle Park, North Carolina 27709	
SIGNATURE: James Crow	DATE: October 15, 2000

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information: Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED:	DUE DATE:	OPDRA CONSULT #:
October 17, 2000	January 22, 2001	00-0283

TO: Raymond Lipicky, M.D.
Director, Division of Cardio-Renal Drug Products
HFD-110

THROUGH: Edward Fromm, Project Manager
HFD-110

PRODUCT NAME:
UNIPROST (Primary)
and REMODULIN (Alternate)

(Treprostinol Sodium Injection)
1 mg/mL, 2.5 mg/mL, 5 mg/mL and 10 mg/mL

NDA #: 21-272

MANUFACTURER: United Therapeutics Corp.

SAFETY EVALUATOR: Carol Holquist, R.Ph.

SUMMARY: In response to a consult from the Division of Cardio-Renal Drug Products (HFD-110), OPDRA nducted a review of the proposed proprietary names "Uniprost" and "Remodulin" to determine the potential for onfusion with approved proprietary and generic names as well as pending names.

OPDRA RECOMMENDATION: OPDRA does not recommend the use of the proprietary name "Uniprost". However, OPDRA has no objection to the use of the proprietary name "Remodulin". In addition, OPDRA recommends implementation of the enclosed labeling revisions in order to minimize the potential for medication errors. See the checked box below.

☐ FOR NDA/ANDA WITH ACTION DATE BEYOND 90 DAYS OF THIS REVIEW
This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDAs from the signature date of this document. A re-review request of the name should be submitted via e-mail to "OPDRAREQUEST" with the NDA number, the proprietary name, and the goal date. OPDRA will respond back via e-mail with the final recommendation.

☒ FOR NDA/ANDA WITH ACTION DATE WITHIN 90 DAYS OF THIS REVIEW
OPDRA considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from this date forward.

FOR PRIORITY 6 MONTH REVIEWS
OPDRA will monitor this name until approximately 30 days before the approval of the NDA. The reviewing division need not submit a second consult for name review. OPDRA will notify the reviewing division of any changes in our recommendation of the name based upon the approvals of other proprietary names/NDAs from this date forward.

/S/

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
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/S/

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Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm. 15B03
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: **January 9, 2001**

NDA NUMBER: **21-272**

NAME OF DRUG: **UNIPROST (Primary) and REMODULIN (Alternate)**
(Treprostinol Sodium Injection)
1 mg/mL, 2.5 mg/mL, 5 mg/mL and 10 mg/mL

NDA HOLDER: **United Therapeutics Corp.**

I. INTRODUCTION

This consult was written in response to a October 16, 2000, request from the Division of Cardio-Renal Drug Products (HFD-110), for assessment of the proposed proprietary drug name, Uniprost and alternate name, Remodulin, regarding potential name confusion with other proprietary/generic drug names.

PRODUCT INFORMATION

Uniprost/Remodulin contains the active ingredient tresprotinol sodium. Tresprotinol is a tricyclic benzidene analogue of prostacyclin (PGI_2) with potent pulmonary and systemic vasodilatory activity. It is also a potent inhibitor of platelet aggregation. The vasodilatory effects reduce right and left ventricular afterload and increase cardiac output and stroke volume. Uniprost/Remodulin is indicated for the long-term subcutaneous treatment of Pulmonary Arterial Hypertension in New York Heart Association (NYHA) Class II, III, and IV patients. Uniprost/Remodulin is administered by subcutaneous infusion, via a self-inserted subcutaneous catheter, using an infusion pump designed for subcutaneous drug delivery. The dosage is initiated at 1.25 ng/kg/min. If this initial dose cannot be tolerated, the dosage should be reduced to 0.625 ng/kg/min. The infusion rate is calculated using the following formula:

Infusion rate (mL/hr) = Dose (ng/kg/min) x Weight (kg) x [0.00006/Uniprost concentration (mg/mL]

The infusion rate is adjusted based on Pulmonary Arterial Hypertension (PAH) signs and symptoms and drug side effects. The product will be supplied in 20 mL vials with the following concentrations: 1 mg/mL, 2.5 mg/mL, 5 mg/mL, and 10 mg/mL.

II. RISK ASSESSMENT

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts[i,ii,iii] as well as several FDA databases[iv] for existing drug names which sound alike or look alike to Uniprost and Remodulin to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[v]. An Expert Panel discussion was conducted to review all findings from the searches. In addition, OPDRA conducted six prescription analysis studies, to simulate the prescription ordering process.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by OPDRA to gather professional opinions on the safety of the proprietary names Uniprost and Remodulin. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of OPDRA Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

Several products were identified in the Expert Panel Discussion that was thought to have potential for confusion with Uniprost and/or Remodulin. These products are listed in Table 1, along with the dosage forms available and usual FDA-approved dosage. The panel also expressed their preference for Remodulin due to the numerous products currently marketed with the prefix "Uni".

DDMAC did not have any concerns with regard to promotional claims for either name.

[i] MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Co. Inc, 2000).

[ii] American Drug index, 42nd Edition, 1999, Facts and Comparisons, St. Louis, MO.

[iii] Facts and Comparisons, 2000, Facts and Comparisons, St. Louis, MO.

[iv] COMIS, The Established Evaluation System [EES], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug Approvals 98-00, and online version of the FDA Orange Book.

[v] WWW location http://www.uspto.gov/tmdb/index.html.

TABLE 1

Product Name	Dosage form(s), Generic name	Usual adult dose*	Other**
Uniprost/Remodulin	Triprostinol Injection, 20 mL vial – 1 mg/mL, 2.5 mg/mL, 5 mg/mL and 10 mg/mL	1.25 ng/kg/min, if not tolerated the dose is reduced to 0.625 ng/kg/mm.	
Unipres	Tablet, Hydralazine HCl, Hydrochlorothiazide and Reserpine 25 mg/15 mg/0.1 mg	1 or 2 tablets 3 times a day.	S/A, L/A per OPDRA
Uniphyl	Theophylline Tablet, 400 mg and 600 mg	Once daily in the morning or evening.	S/A, L/A per OPDRA
Unipen	Nafcillin Sodium 500 mg Tablets, 250 mg Capsules, 2 g ADD-Vantage Vials and 1 g and 2 g premixed Piggybacks	*Adults Oral* – 250 mg to 500 mg q 4-6 h and 1 g q 4-6 h. *IM* – 500 mg q 4-6 h. *IV* – 1-2 g q 4-6 h. *Pediatric Oral*: 30-40 mg/kg daily given in 3 to 4 equally divided doses. *IM*: 50 mg/kg/day in 2 divided doses. *IV*: 100-200 mg/kg daily in equally divided doses q 4 –6 h.	S/A, L/A per OPDRA
Uniplus	Propyphenazone, Oral and Rectal	Available in Europe only.	S/A, L/A per OPDRA
Remedeline	Paracetamol; dihydrododeine tartrate	Available in the UK only.	S/A, L/A per OPDRA
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike)			

B. STUDY CONDUCTED BY OPDRA

1. Methodology

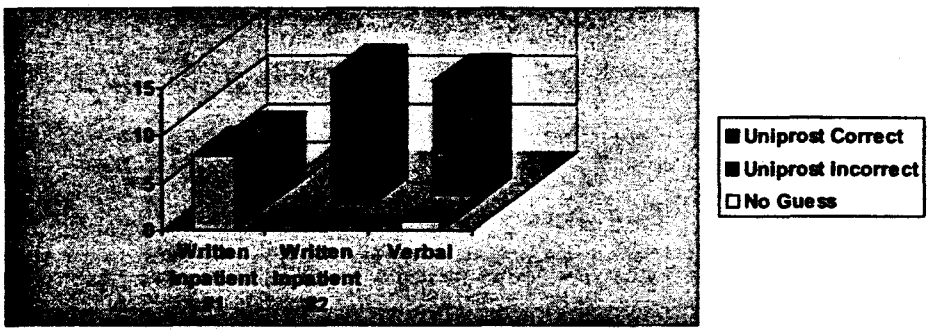
Six separate studies were conducted within FDA, to determine the degree of confusion of Uniprost and Remodulin with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug names. These studies employed a total of 87 health care professionals (nurses, pharmacists, and physicians). This exercise was conducted in an attempt to simulate the prescription ordering process. An OPDRA staff member wrote two inpatient orders, each consisting of a combination of marketed and unapproved drug products and prescriptions for Uniprost and Remodulin (see page 5). These written prescriptions were optically scanned and one prescription was delivered via email to each study participant. In addition, one OPDRA staff member recorded a verbal inpatient prescription that was then delivered to a group of study participants via telephone voicemail. Each reviewer was then requested to provide an interpretation of the prescription via email.

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTIONS
UNIPROST	
Inpatient #1: Uniprost ↑ to 2.5 ng/kg/min	*Inpatient:* Increase Uniprost to 2.5 nanograms/kilogram/minute
Inpatient #2: Uniprost – increase to 2.5 ng/kg/min	
REMODULIN	
Inpatient #1: ↑ Remodulin to 2.5 ng/kg/min	*Inpatient:* Increase remodulin to 2.5 nanograms/kilogram/minute
Inpatient #2: ↑ Remodulin to 2.5 ng/kg/min	

2. Results

Results of these exercises are summarized below:

Study	No. of participants	# of responses (%)	"Uniprost" response	Other response
Written: Inpatient #1	29	16 (55%)	8 (50 %)	8 (50 %)
Inpatient #2	28	14 (50 %)	0 (0 %)	14 (100 %)
Verbal: Inpatient	30	14 (47 %)	1 (7 %)	13 (93 %)
Total:	87	44 (51 %)	9 (20 %)	35 (80 %)
Study	No. of participants	# of responses (%)	"Remodulin" response	Other response
Written: Inpatient #1	29	19 (66 %)	18 (95 %)	1 (5 %)
Inpatient #2	30	15 (50 %)	15 (100 %)	0 (0 %)
Verbal: Inpatient #1	28	11 (39 %)	4 (36 %)	7 (64 %)
Total:	87	45 (52 %)	37 (82 %)	8 (18 %)



Among participants in the written prescription studies for Uniprost, 22 of 30 respondents (73 %) interpreted the name incorrectly. The majority of incorrect responses were misspelled variations of "Uniprost". *Seven* respondents misinterpreted Uniprost as Unipast, misinterpreting the "o" as an "a". *Five* respondents provided Unipost as an interpretation, eliminating the "r" in the name, and *four* respondents misinterpreted Uniprost as Uniprest, misinterpreting the "o" as an "e". Other interpretations include: Uniprst, unyscot, uniprot, uvipost and uvipast.

Among participants in the verbal prescription study for Uniprost, 13 of 14 (93 %) participants interpreted the name incorrectly. *One* participant interpreted the name as Unipres. *Three* interpreted the name as Unipros, *two* as Unapros, two as Xenoprost.

Among participants in the written prescription studies for Remodulin, 2 of 34 respondents (6 %) interpreted the name *incorrectly*. The incorrect name interpretations were misspelled variations of "Remodulin".

Among participants in the verbal prescription study for Remodulin, 7 of 11 (64 %) interpreted the name incorrectly. The majority of the incorrect name interpretations were phonetic variations of "Remodulin". The prefix "Rem" was misinterpreted as "Imm", "Herm", "Mod" and "Amo". The suffix "dulin" was misinterpreted as "dulan", "dulen" and "golin".

C. SAFETY EVALUATOR RISK ASSESSMENT

1. Uniprost

In reviewing the proprietary name "Uniprost", the primary concerns raised were related to several sound-alike/look-alike names that already exist in the U.S. marketplace. Unipres, Uniphyl and Unipen were considered to be the most problematic in terms of their potential for medication errors.

We conducted prescription studies to simulate the prescription ordering process. In this case, there was confirmation that *Uniprost* could be confused with *Unipres*. *One* respondent provided Unipres as an interpretation from a verbal order. *Unipres* is an oral tablet indicated for the treatment of hypertension that contains a fixed combination of 0.1 mg of reserpine, 25 mg of hydralazine and 15 mg of hydrochlorothiazide. Unipres has been discontinued yet the name still appears in standard drug reference texts and databases. Post-marketing experience has demonstrated product confusion among drug products that have been discontinued from the marketplace but remain in common drug reference texts. In these post-marketing cases, practitioners unfamiliar with the new trade name research the name in a standard drug reference and often dispense the generic of the discontinued product. Despite these instances where confusion has occurred, OPDRA believes the risk for confusion between Unipres and Uniprost is relatively low. The verbal order for Uniprost in the OPDRA study was delivered as "Increase Uniprost to 2.5 nanograms/kilogram/minute". One participant interpreted this as Unipres. However, Unipres could never be administered as ordered. Unipres was never available in an injectable form and therefore a generic substitution would not be possible. Uniprost also differs from Unipres in dosage form, dosing interval, and indications for use.

Uniphyl is the proprietary name for theophylline, which is a controlled release tablet that allows a 24 hour dosing interval for appropriate patients. Theophylline is indicated for the treatment of the symptoms and reversible airflow obstruction associated with chronic asthma and other chronic lung diseases. Uniphyl is available as 400 mg and 600 mg tablets. The potential for patient harm would be significant if the two drug products were confused. However, given the differences in dosage form, dosing intervals, and product administration we believe the risk for confusion is relatively low.

Unipen is the proprietary name for nafcillin sodium, which is a semisynthetic penicillinase-resistant penicillin. Unipen is commercially available in oral, intramuscular and intravenous dosage forms. The dosage varies dependent on the severity of infection and route of administration. The two products look similar when scripted because they begin with the same letters, "Unip". Often when prescriptions are scripted the suffix of the name is scribbled making it difficult to discern the trailing letters. Moreover, the two products are available in a parenteral dosage form and pediatric dosages of Unipen are calculated on a mg/kg/day basis. Milligrams and nanograms could easily be confused for one another when scripted. If a medication misadventure were to occur between these two drug products it could result in serious injury (i.e. anaphylactic shock due to a penicillin allergy).

OPDRA is also concerned with the potential for confusion between Uniprost and the established name Unoprostone. Unoprostone is the established name for Rescula, an ophthalmic solution indicated for the lowering of intraocular pressure in patients with open-angle glaucoma or ocular hypertension who are intolerant of other intraocular pressure lowering medication or insufficiently responsive to another intraocular pressure lowering medication. Uniprost and Uniprostone sound similar and look similar when scripted differing only by the last three letters. These two products could be confused on an inpatient order because drugs are routinely prescribed utilizing the established name rather than the trade name in hospitals and long term care facilities. Unoprostone has been reported to cause changes to pigmented tissue and these changes may be permanent. In addition, patients might experience an allergic reaction to the preservative or active ingredient itself.

In addition, the proprietary name Uniprost contains "prost" which is a United States Adopted Names Council (USAN) stem for prostaglandin derivatives. Uniprost is a prostaglandin derivative and therefore we have no objections to the use of the USAN stem.

2. Remodulin

In reviewing the proprietary name "Remodulin", the primary concern raised was related to one sound-alike, look-alike name for a drug product that is currently marketed only in the United Kingdom, "Remedeline". There is limited product information available on Remedeline.

We conducted prescription studies to simulate the prescription ordering process. In this case, there was *no* confirmation that Remodulin could be confused with Remedeline. The majority of incorrect responses were misspelled phonetic variations of Remodulin. No currently marketed drug products were provided as an interpretation. Although a negative finding in a study with such a small sample size does limit its predicative value, OPDRA believes the potential for confusion is low.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

In the review of the container labels, carton labeling, and draft package insert for Uniprost, OPDRA has attempted to focus on safety issues relating to possible medication errors. We have identified several areas of possible improvement, in the interest of minimizing potential user error. OPDRA utilized the approved labeling of NDA 20-444, Flolan (Epoprostenol Sodium for Injection) as a model for the proposed labeling of this drug product. Flolan is an injectable prostaglandin indicated for the treatment of Pulmonary Hypertension as well. In order to minimize user error, OPDRA believes the labeling of these products should be consistent due to the unconventional method in which the strengths are expressed and the unusually small doses that are prescribed.

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

v. The "Administration" subsection of the insert is extremely specific with regard to the type of infusion pump needed for the proper delivery of this drug product. The sponsor should provide the name of a pump that fits this description in order to assure the patient or practitioner purchases a model that will meet these specific criteria.

vi. The Dosage and Administration section does not provide adequate directions for use. How is the drug prepared for administration? Can the drug be administered without requiring further dilution? What type of container is utilized for the delivery of the drug product (i.e., IV bag, drug cassette, and syringe)? Is the final product prepared and dispensed from a pharmacy or will patients be required to prepare the dose for administration?

There is also no discussion as to which concentration is the most suitable to use to deliver the initial dose of 1.25 ng/kg/min.

IV. RECOMMENDATIONS

OPDRA does not recommend the use of the proprietary name "Uniprost". OPDRA has no objection to the use of the proprietary name "Remodulin". OPDRA also recommends implementation of the above labeling revisions in order to minimize the potential for medication errors.

OPDRA would appreciate feedback of the final outcome of this consult. We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact the project manager, Sammie Beam, R.Ph., at 301-827-3231.

/S/

Carol Holquist, R.Ph.
Safety Evaluator
Office of Postmarketing Drug Risk Assessment (OPDRA)

Concur: /S/

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Postmarketing Drug Risk Assessment (OPDRA)

/s/

Carol Holquist
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Jerry Phillips
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Martin Himmel
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MEDICAL OFFICER

Minutes of a Meeting between United Therapeutics and the FDA

Date: March 28, 2002

Applications: NDA 21-272
Remodulin (treprostinil sodium) Injection

Applicant: United Therapeutics Co.

Subject: Discussion of Post-Marketing Study

FDA Participants:

Robert Temple, M.D., HFD-101, Director, Office of Drug Evaluation and Research
Douglas C. Throckmorton, M.D., HFD-110, Acting Division Director
Norman Stockbridge, M.D., Ph.D., Medical Team Leader
James Hung, Ph.D., HFD-110, Statistician/Team Leader
John Lawrence, Ph.D., HFD-110, Statistician
Ms. Natalia A. Morgenstern, HFD-110, Chief, Project Management Staff (pre-meeting only)
Mr. Edward Fromm, HFD-110, Regulatory Health Project Manager

United Therapeutics

Roger Jeffs, Ph.D., President and Chief Operating Officer
Mr. Dean Bunce, Senior Director, Regulatory Affairs
Mr. Carl Arneson, Manager of Biostatistics and Data Management
Mr. Jeff Sigman, Senior Clinical Research Associate
Michael Wade, Ph.D., Associate Director, Research and Development

Background

Remodulin (treprostinil sodium) Injection was issued an approvable letter under subpart H on February 8, 2002 for the treatment of pulmonary arterial hypertension (PAH).

A condition of the approvable letter was a post-approval controlled clinical trial that would test the effects of Remodulin on endpoints that are clearly clinically relevant. At a meeting on February 13, 2002, the sponsor and the Agency reached an agreement in principle that a trial withdrawing patients from Flolan and assigning them, in a randomized manner, to either Remodulin or placebo and measuring a primary end point of death or clinical deterioration of PAH symptoms, would be sufficient to assess the clinical benefit of Remodulin and, upon successful completion, would satisfy that commitment of the approvable letter. Note that we expected to see no deaths in such a study; patients would be carefully monitored for signs of deterioration.

The meeting today is to discuss revisions to the proposed protocol (P01:13), "*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*", that the Agency suggested at the March 7, 2002 meeting and whether they were sufficient to satisfy that condition of the approvable letter.

Meeting

Post-Approval Study

Events to be sent to the Adjudication Committee

Dr. Temple opened the meeting by noting that in the context of the primary endpoint of the worsening of PAH symptoms leading to death, rehospitalization, and reinstitution of therapy, the Agency is unclear what information regarding clinical events will be sent from investigators to the Adjudication Committee. The sponsor replied that the Adjudication Committee would only receive information pertaining to the event; this would include a narrative of the event by the investigator that would also outline the sequence of that event. Dr. Throckmorton said that all patients discontinued from the study should be sent to the Adjudication Committee. The sponsor asked if this would include patients who needed reinstitution of Flolan during the withdrawal phase. Dr. Temple said it would and that from the narratives of these events the Adjudication Committee would have a clear idea of the description and timeline of the actual event(s). He added that the narratives should omit any reference to infusion site pain.

Dr. Temple asked if there would be a structured assessment any time a patient is discontinued from the study. The sponsor said that in the protocol there are a number of assessments that measure patient's symptoms (e.g., dypsnea, fatigue) at the time of discontinuation from the study.

Flolan Withdrawal Symptoms

Dr. Temple emphasized that we wanted to be able to distinguish a withdrawal phenomenon from simple worsening due to drug withdrawal. Slow withdrawal should reduce the likelihood of a withdrawal effect. In addition, patients might be given the opportunity to go back on Flolan if there are symptoms. After that tapering would be resumed. The sponsor replied it was uncertain how the first event would be counted and could also introduce unblinding for that event. Moreover, the withdrawal symptoms might be so severe after the first time off Flolan that the investigator would be very hesitant about repeating the process again. Dr. Temple agreed that it was not reasonable to subject the patient and investigator to this potential problem if symptoms were severe, but it could be done for lesser symptoms.

Dr. Temple said it was his understanding that the symptoms from withdrawal from Flolan generally occur only after all of the drug has been removed from the patients. Therefore, it might be helpful to leave a little drug (e.g., 2 ng/kg/min) on board to prevent these symptoms (rebound effect) as well as to help distinguish them from loss of benefit of Flolan. United Therapeutics said that they believe that the rebound effects will occur well before the last 2 ng/kg/min are withdrawn, although there are no clear data on this. They proposed that the slow tapering of drug in the withdrawal phase of the study as well as extending the time the patients receive 5% of the starting dose of Flolan for an additional 2 days (a total of 3 days) should minimize this problem. Dr. Temple said this was acceptable so long as any withdrawal event was fully described so the Adjudication Committee could consider it.

Formal Commitment Letter

Dr. Throckmorton said the sponsor should make the above revisions to their protocol and submit it for review. If the Division deems the protocol acceptable this submission will constitute a "complete response" to the approvable letter of February 8, 2002. He requested that United Therapeutics submit a letter formally committing to the timelines for completing the post-approval study outlined in the approvable letter. The sponsor said they would send in the revised protocol and formally commit to the timelines noted in the approvable letter for completion of the post-approval study.

Summary of Main Action Items

- The sponsor will revise the protocol so that the Adjudication Committee will review all discontinuations from study drug and all reinstitution of Flolan Therapy for any reason.
- The sponsor will continue 5% of the starting dose of Flolan for 3 days (2 more than the current protocol) to minimize potential rebound effects.
- United Therapeutics will submit a revised protocol and commitment to meet the guidelines for completion of the post-approval study outlined in the approvable letter.

Minutes Preparation: /S/
Edward Fromm

Concurrence Chair: /S/
Robert Temple, M.D.

ef/dr-4/3/02-4/9/02

Rd: JHung-4/3/02
JLawrence-4/3/02
NStockbridge-4/4/02
DThrockmorton-4/4/02

Minutes of a Meeting between United Therapeutics and the FDA

Date: March 7, 2002

Applications: NDA 21-272
Remodulin (treprostinil sodium) Injection

Applicant: United Therapeutics Co.

Subject: Discussion of Post-Marketing Study

FDA Participants:

Robert Temple, M.D., HFD-101, Director, Office of Drug Evaluation and Research
Douglas Throckmorton, M.D., HFD-110, Acting Division Director
Norman Stockbridge, M.D., Ph.D., Medical Team Leader
Abraham Karkowsky, M.D., Ph.D., HFD-110, Medical Team Leader
James Hung, Ph.D., HFD-110, Statistician/Team Leader
John Lawrence, Ph.D., HFD-110, Statistician
Ms. Natalia A. Morgenstern, HFD-110, Chief, Project Management Staff
Mr. Edward Fromm, HFD-110, Project Manager

United Therapeutics

Roger Jeffs, Ph.D., President and Chief Operating Officer
Mr. Dean Bunce, Senior Director, Regulatory Affairs
Mr. Carl Arneson, Manager of Biostatistics and Data Management
Mr. Paul Mahon, J.D., General Counsel
Mr. Kerry McKenzie, Regulatory Associate
David Mottola, M.D., Vice President of Clinical and Scientific Affairs
Ms. Lavonne Stagg-Hope, Senior Regulatory Coordinator
Michael Wade, Ph.D., Associate Director, Research and Development
Mr. Frank Sasinowski, Regulatory Consultant
Mr. Jeff Sigman, Senior Clinical Research Associate

Background

Remodulin (treprostinil sodium) Injection was issued an approvable letter under subpart H on February 8, 2002 for the treatment of pulmonary arterial hypertension (PAH).

A condition of the approvable letter was a post-approval controlled clinical trial that would test the effects of Remodulin on endpoints that are clearly clinically relevant. At a meeting on February 13, 2002, the sponsor and the Agency reached an agreement in principle that a trial withdrawing patients, in a randomized manner, from Flolan and randomly assigning them to either Remodulin or placebo and measuring a primary end point of death or clinical deterioration of PAH symptoms, would be sufficient to demonstrate the clinical benefit of Remodulin and, upon successful completion, would satisfy that commitment of the approvable letter. Note that we expected to see no deaths in such a study; patients would be carefully monitored for signs of deterioration.

The meeting today is to discuss revisions to the proposed protocol that the Agency suggested at the last meeting and whether they were sufficient to satisfy that condition of the approvable letter. In addition, the sponsor plans to submit information confirming that a sufficient number of investigators and institutions are ready to begin the above-mentioned trial.

Meeting

Post-Approval Study

Dr. Temple opened the meeting by noting that we have identified several potential problems with the protocol the sponsor submitted after the last meeting. They are:

- Potential rebound PAH symptoms from too rapid withdrawal from Flolan therapy. We think the down-titration phase should be slower than what the sponsor proposes. Our concern is mainly with the treatment group that is randomized to placebo and thus would be most at risk for developing rebound PAH symptoms. Dr. Temple thought a withdrawal period of about 10-14 days in an institutional setting would avoid this problem. A slower weaning period would also help limit confusion over the effect of Remodulin when rebound occurs. To prevent further renewal of symptoms as patients are being weaned off Flolan, consideration should be given to front-loading the initial phases of the study with a higher dose of Remodulin. Dr. Temple suggested that the firm also include in their protocol a means of temporarily increasing the dose of Flolan in patients that are having difficulty weaning off of it.

  United Therapeutics agreed to slow the down-titration phase of the trial and said it was exploring the idea of decreasing Flolan in 2.5 ng/kg/min increments as opposed to the 5.0 ng/kg/min increments proposed before. They noted that they would submit a revised proposal for down-titrating patients from Flolan shortly.

- Definition of reinstitution of therapy. Dr. Temple said the sponsor would need to define further the "need for reinstitution of therapy" component of the primary endpoint. One suggestion might be for the patient to fill out a symptom assessment sheet when down-titration from Flolan is no longer possible. The sponsor should submit a proposal outlining how they would handle patients in this or a similar situation.

- Infusion site pain and blinding. Dr. Temple noted that although it might be difficult, the sponsor should try to obtain an exercise test as close as possible to the time a patient drops out of the study. An assessment form should also be developed that would allow patients to describe their symptoms as they are leaving the study. Dr. Karkowsky noted that a large number of dropouts could make the study not interpretable. The sponsor said they are trying to address this problem by noting in the informed consent that patients should expect infusion pain regardless of the treatment given. Dr. Throckmorton noted that narcotic use data by patients in the study should also be collected.

  United Therapeutics said that to further alleviate the Agency's concerns about blinding in the study due to infusion site pain, they will redesign the Case Report Form (CRF) to include multiple assessments that will define in detail the reason for a patient leaving the trial. The CRFs for all patient dropouts will then be forwarded to an Adjudication Committee that will review them in one meeting. Dr. Temple said the sponsor's proposal was acceptable.

- Definition of hospitalizations. Dr. Karkowsky suggested that the sponsor identify hospitalizations that should not be counted as part of the primary endpoint (e.g., elective surgeries).

- Flolan arm. Dr. Temple said we expect little clinical deterioration in patients that are randomized to the Remodulin arm but if this happens the study could yield an ambiguous result. The adding of a Flolan only arm to the study would serve as a control in case an unexpected number of patients show clinical

deterioration while receiving Remodulin. The sponsor replied that they would consider the Agency's suggestion, but believe that very few, if any patients will dropout due to clinical deterioration while on Remodulin.

Labeling

United Therapeutics noted they had sent in revised labeling in response to the Agency's marked-up draft labeling included in the approvable letter and asked if the Agency could provide any feedback on it. Mr. Fromm replied that the Division had further revised the labeling and a copy of those revisions would be provided at the end of today's meeting. Dr. Temple, however, might make additional revisions and these would be sent to the sponsor as soon as they are available.

The sponsor asked at what point would the PDUFA 2 month review clock begin. Dr. Temple replied that once there was mutual agreement regarding the commitments of the approvable letter (i.e., post-approval study design, list of investigators and sites, and labeling), then the sponsor could send in final printed labeling and the review clock would be activated. The sponsor said they would send in a revised protocol shortly along with a list of investigators and sites that have agreed to participate in the study.

Summary of Main Action Items

- The sponsor will address the Agency's concern regarding too rapid a withdrawal from Flolan therapy. The protocol should also be modified to include a provision for up-titrating the dose of patients that are having difficulty weaning off Flolan therapy.
- The sponsor will further define the endpoint of "need for reinstitution of therapy."
- The sponsor will identify hospitalizations that it believes should not be considered related to PAH.
- The sponsor will develop a CRF that will accurately describe the reasons for patients leaving the study.
- The Agency suggested a Flolan only arm to the study if the sponsor believes that some patients may show clinical deterioration while on Remodulin.
- Dr. Temple will likely make additional revisions to the labeling that will be sent to the sponsor as soon as they are available.

Minutes Preparation: /S/
Edward Fromm

Concurrence Chair: /S/ 3/21/02
Robert Temple, M.D.

ef/dr-3-11-02/3-19-02/3-21-02

Rd: JLawrence-3-11-02
JHung-3-12-02
NStockbridge-3-15-02
AKarkowsky-3-15-02
DThrockmorton-3-15-02
NMorgenstern-3-15-02

Minutes of a Meeting between United Therapeutics and the FDA

Date: February 13, 2002

Applications: NDA 21-272
Remodulin (treprostinil sodium) Injection

Applicant: United Therapeutics Co.

Subject: Discussion of Post-Marketing Study

FDA Participants:

Robert Temple, M.D., HFD-101, Director, Office of Drug Evaluation and Research I
Raymond Lipicky, M.D., HFD-110, Director, Division of Cardio-Renal Drug Products
Douglas Throckmorton, M.D., HFD-110, Deputy Division Director
Norman Stockbridge, M.D., Ph.D., HFD-110, Medical Team Leader
Abraham Karkowsky, M.D., Ph.D., HFD-110, Medical Team Leader
James Hung, Ph.D., HFD-110, Statistician/Team Leader
John Lawrence, Ph.D., HFD-110, Statistician
Nhi Nguyen, Pharm.D., HFD-860, Clinical Pharmacology and Biopharmaceutics
Natalia Morgenstern, HFD-110, Chief, Project Management Staff
Edward Fromm, HFD-110, Project Manager

United Therapeutics

Roger Jeffs, Ph.D., President and Chief Operating Officer
Dean Bunce, Senior Director, Regulatory Affairs
Carl Arneson, M.Stat, Manager of Biostatistics and Data Management

Paul Mahon, J.D., General Counsel
Kerry McKenzie, Regulatory Associate
David Mottola, Ph.D., Vice President of Clinical and Scientific Affairs
Lavonne Stagg-Hope, Senior Regulatory Coordinator
Michael Wade, Ph.D., Associate Director, Research and Development

Background

Remodulin (treprostinil sodium) Injection was issued an approvable letter on February 8, 2002 for the treatment of pulmonary arterial hypertension (PAH). Specifically, the drug 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 but is not as well-established as a clear effect on exercise alone. The effect of Remodulin on exercise was statistically marginal. Therefore a post-approval, controlled clinical trial is needed to test the effects of Remodulin on end points that are clearly clinically relevant.

The approvable letter outlined two possible trial designs that would test the effect of Remodulin on clinical end points. The meeting today is to discuss those designs and any others that would lead to an agreement between United Therapeutics and the Division on single, post-marketing trial that would unambiguously demonstrate the benefit of Remodulin on clinically relevant end points.

Meeting

Post-Approval Study Design

Dr. Temple opened the meeting by noting that the approvable letter sent to the sponsor outlined two possible post-approval study designs that would confirm the clinical benefit of the drug. Our study preference is the add-on of Remodulin to bosentan, as it could show improvement over the currently available treatment. The sponsor replied that they had considered this option, but believe, based on their surveys of the marketplace, that very few patients are so far using bosentan in the United States or worldwide. Furthermore, it would be necessary to find patients that are taking bosentan and are still symptomatic. Dr. Temple noted that recruitment may be difficult for this trial and therefore the Agency is amenable to changing the time guidelines for completing the study outlined in the approvable letter. He added that the sponsor should document to the Agency why patients cannot be recruited for the bosentan trial.

United Therapeutics said that the randomized, withdrawal study from treprostinil to placebo or tapering doses of treprostinil mentioned in the approvable letter was considered but deemed not feasible because it would be difficult to motivate patients to withdraw from their current therapy. Instead, the sponsor is proposing a variation of that study that they think will have better patient acceptance. In this study, patients who are currently taking Flolan (epoprostenol) would be carefully down-titrated from Flolan (to avoid a rebound effect) and randomized on a 1:1 basis to either Remodulin or placebo. Randomization may be stratified by dose at baseline. Patients entering the study would have to be clinically stable on Flolan for PAH symptoms for the previous 30 days and would be subject to intensive monitoring in a hospitalized setting. A DSMB (Data Safety Monitoring Board) independent of the sponsor would monitor the study for safety and efficacy. The sponsor noted that a patient receiving a very high dose of Flolan (e.g., 100 ng/kg/min) might take up to 6 days to be completely withdrawn from the drug.
Dr. Throckmorton asked if the down-titration scheme proposed by the sponsor is consistent with instructions in the current labeling for Flolan. The sponsor replied that the current label only mentions that "withdrawal of the drug be done under close supervision of a physician."

United Therapeutics said that the primary endpoint of the trial would be a time-to-event analysis of death, or clinical deterioration, defined as worsening of PAH symptoms leading to either:

- reinstitution of therapy, or
- hospitalization.

Dr. Temple noted that we did not expect properly followed patients to die, that is, deterioration (renewed symptoms) should occur well before serious injury. The study is acceptable (removing people from apparently effective therapy) because Flolan has significant risks and is difficult to use. United Therapeutics said patients will be followed for 12 weeks or until time of death or clinical deterioration. Dr. Throckmorton asked how reinstitution of therapy would be defined. The sponsor said that Flolan would be the drug of choice if reinstitution of therapy were needed, although they would like the Agency to consider the use of Remodulin for those placebo patients that are showing signs of deterioration. Dr. Throckmorton replied that the promise of Remodulin as a rescue treatment might cause some patients to overstate their symptoms, which would inflate the failure rate in the placebo group. Dr. Temple noted, however, that it is certainly permissible for the sponsor to offer Remodulin to the patients after the study is completed. He added that although patients stabilized on Flolan are acceptable as the focus of the withdrawal study, the sponsor should also consider bosentan failures as candidates.

Dr. Lipicky noted that the sample sizes proposed for the Flolan withdrawal study are very small and therefore the sponsor should consider a p value not around the margins of the traditional $p<0.05$ for a single trial, but in the range of $p<0.01$. United Therapeutics agreed, but noted that the trial would be event-rate driven; either using a placebo event rate or a total event rate. Dr. Temple said that he is not sure that a time-to-event analysis is most appropriate for this trial; for example, what if patients are unable at 3 weeks to continue therapy because of infusion site pain. How would these patients be counted? The sponsor replied that they would not be counted as

failures as there could be some beneficial effect on the clinical events of PAH. Dr. Karkowsky argued these patients should be followed to the end of the study but considered failures at the time point they required Flolan. Dr. Temple said that a true intent-to-treat analysis may not be appropriate for a trial with symptomatic end points, and said that patients who dropout from the study due to intolerance should not be counted as failures at that point (i.e., meeting an end point). Nevertheless, the Agency needs assurance that these patients are not dropping out for any other reason other than intolerance to the drug.

The sponsor suggested that patients who are intolerant to Remodulin could be started on open-label Flolan and kept in the study. Dr. Temple disagreed, noting that this could overstate Remodulin's benefit (if in fact they were also symptomatic from PAH) and would make interpretation of the data difficult. United Therapeutics proposed that a solution to the issue of patients who drop out due to intolerance of Remodulin would be to collect information on why patients dropped out and then ask that the DSMB adjudicate these data. Dr. Temple replied that the collection of these data would be useful and suggested that to help limit the patients who might drop out due to intolerance, the informed consent should be modified to warn patients of possible infusion site pain and the availability of pain medications in case this occurs. The sponsor should address the intolerance issue in detail when they submit their draft protocol to the Division for review. They should also include information on how Remodulin will be down-titrated once the study is completed.

Stopping Rules

United Therapeutics asked what stopping rules should the DSMB use for stopping the Flolan withdrawal trial. Dr. Temple replied that they should not stop before the end of the trial unless it is apparent that the drug is causing irreversible harm. We do not think this will occur if patients are properly monitored.

Identifying Investigators

The sponsor noted that the approvable letter mentioned that the investigators for the post-marketing trial would have to be identified before approval could be granted and asked how they could document this to the Agency. Dr. Lipicky said that they should identify in detail the sites and investigators for the study, but that they did not have to wait for IRB (Institutional Review Board) approval before submitting this information to the Division.

Labeling

The sponsor said that they have reviewed the marked-up draft labeling that accompanied the approvable letter and said there were few disagreements to what the Agency proposed. They noted, however, that under the **Clinical Trials** section of the labeling, they would like to add a quantitative description of the Borg/Walk findings. Dr. Temple said that it would probably be difficult to include a true description of these findings in the labeling but invited the sponsor to submit their proposal for review. DDMAC (Division of Drug Marketing, Advertising, and Communications) would also be involved in the review of this submission.

United Therapeutics asked that under the **Clinical Trials** section, a description of the secondary findings be allowed. Dr. Temple said a general statement about symptoms such as dyspnea and fatigue could be given but not the entire list of secondary findings, as the blinding of these analyses was uncertain.

Conclusion

United Therapeutics and the Agency reached an agreement in principle that a trial withdrawing patients, in a randomized manner, from Flolan to either Remodulin or placebo and measuring a primary end point of death or clinical deterioration of PAH symptoms, would be sufficient to demonstrate the clinical benefit of Remodulin and, upon successful completion, would satisfy that commitment of the approvable letter.

The sponsor was encouraged to submit a draft protocol of the proposed Flolan trial, and in particular address the issue of how patients will be handled if they drop out of the study due to intolerance to Remodulin. The sponsor should also modify the informed consent form by explaining that infusion pain is a possible side effect of Remodulin therapy but that pain medications, including narcotics would be available to ameliorate this pain.

Minutes Preparation: /S/
Edward Fromm

Concurrence Chair: /S/
Robert Temple, M.D.

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AKarkowsky-2/19/02
NStockbridge-2/22/02
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NMorgenstern-2/22/02

linutes of a Meeting between United Therapeutics and the FDA

Date: June 22, 2001

Applications: NDA 21-272
Remodulin (treprostinil sodium) Injection

Applicant: United Therapeutics

Subject: Agency Feedback on Approvability of the Drug

FDA Participants:

Robert Temple, M.D., HFD-101, Director, Office of Drug Evaluation and Research I
Douglas Throckmorton, M.D., HFD-110, Deputy Division Director
Abraham Karkowsky, M.D., Ph.D., HFD-110, Medical Team Leader
James Hung, Ph.D., HFD-110, Statistician/Team Leader
John Lawrence, Ph.D., HFD-110, Statistician
Nhi Nguyen, Pharm.D., HFD-860, Clinical Pharmacology and Biopharmaceutics
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Roger Jeffs, Ph.D., President and Chief Scientific Officer
James Crow, Ph.D., President Emeritus
Dean Bunce, Director, Regulatory Affairs
Carl Arneson, M.Stat, Manager of Biostatistics and Data Management

Remodulin was submitted as NDA 21-272 on October 16, 2000 for the treatment of pulmonary arterial hypertension (PAH). The drug was granted a priority review with a user fee goal date of April 16, 2001.

The firm met with the Agency on April 11, 2001 to discuss the Agency's regulatory decision as well as other issues relating to the review of the application. At that meeting they were informed that there was insufficient evidence to support approval of the application.

The firm believed that other statistical reanalyses of the data, to reflect both walking distance and dyspnea, could add robustness to the Borg Dypsnea/Walk distance integrated data. Dr. Temple encouraged the firm to send in these reanalyses to the Division, and noted that if the Division received them prior to the (April 16, 2001) goal date, the Agency would classify that response as a major amendment to the NDA. Consequently, the review clock would be extended by 3 months.

nited Therapeutics, on April 12, 2001, submitted new analyses of the Borg/Walk distance integrated data, which xtended the review clock to July 16, 2001. Additionally, the firm submitted on May 14 and June 5, 2001,

additional analyses of the Borg Dyspnea scores and information on narcotic analgesic use for the treatment of infusion site pain and site reactions. Included with these submissions were also data on 8 patients the firm says were successfully transitioned from Flolan to Remodulin as well as published literature abstracts of patients that have received the drug.

Subsequent to these submissions, the firm requested a meeting with the Agency to see if the additional analyses would support approval of the application prior to the July 16, 2001 goal date.

Meeting

United Therapeutics opened the meeting by presenting slides that they said showed a treatment effect (when using a combined Walk Distance/Borg Dyspnea ranking) of Remodulin at weeks 1, 6, and 12. They noted that the treatment effect of the drug, although present at week 1, appeared to be enhanced by week 12. Dr. Temple said the treatment effect appeared to be very modest; it is possible that more convincing results could be achieved if the exercise test was conducted differently.

Unblinding and Its Effects on Secondary Endpoints

United Therapeutics said that they disagreed with the Agency's contention that infusion site pain and reactions had potentially led to unblinding that invalidated the secondary symptomatic endpoints of the study. They noted that although 8 symptoms were chosen as secondary endpoints, 3 of them (dyspnea, chest pain, and syncope) were most relevant to the disease. The firm said syncope, in particular, was not likely to be subject to bias. They noted that 7 patients developed syncope in the placebo group that did not have it previously whereas only 1 patient receiving the drug developed it that did not have it previously. They thought it unlikely that knowledge of treatment, even if it did occur, would influence patients to newly report syncope. They also thought new occurrence of chest pain was unlikely to respond to unblinding.

The firm noted that all 8 symptoms studied leaned in favor of the drug and argued that chest pain and syncope were more resistant to bias. Dr. Throckmorton said it would be helpful for the firm to provide more information (e.g., concomitant medications, prior syncope episodes) on the patients who developed syncope during the 12-week study. Data on the symptom of orthopnea should also be provided, as this symptom too may be less subject to reporting bias. Moreover, the specifics of how the symptom data was collected and evaluated (i.e., what the physician asked the patient when completing the Case Report Form) should be sent to the Division. Dr. Temple said we would review these new submissions when they arrived to the Division, although he doubted these would alter the Agency's current thinking on the approvability of the drug.

Severity of Infusion Site Pain and the Use of Analgesics

United Therapeutics said that a recent survey of patients on long-term Remodulin therapy indicated that very few patients were using opioids to control infusion site pain. They also noted that approximately 40% of the centers in the trial did not use opioids. Trial experience seemed to indicate that careful titration of the drug lessened the incidence of analgesic use, although it did not eliminate it altogether. The firm noted that some patients have been receiving the drug for over 3 years and are receiving no analgesics. Dr. Temple said the fact that patients are still using the drug, even while subject to infusion site pain, is comforting to the Agency. Nevertheless, it appears that a sizeable fraction of patients require pain medication and therefore the Agency has to weigh the very modest exercise benefit of the drug versus its risks.

Remodulin Indications

The firm asked if it were possible to indicate Remodulin for the treatment of PAH patients who are not candidates

for Flolan. Dr. Temple said it was not possible because the Agency is unconvinced that Remodulin is efficacious or PAH.

The firm asked if the survival claim in the labeling of Flolan had influenced the Agency's decision to not support approval of Remodulin. Dr. Temple replied that it has not been a significant factor in the decision-making process; if that were a concern it could be managed by labeling.

Advisory Committee Meeting

Dr. Temple said that the approvability decision for Remodulin was a very "close call" for the Agency, especially with the new analyses of the symptom data, which we had previously largely disregarded (with the exception of the Borg/Dyspnea scores). The Agency would like to present Remodulin to the August Cardio-Renal Advisory Committee Meeting to seek its guidance. Unfortunately, the Agency will have to take a regulatory action on the application by July 16, 2001. Dr. Temple said that because the evidence presented to date does not entirely support approval, a not approvable action will likely be taken. Of course, the firm may withdraw the application before the goal date if they believe that preferable. Dr. Temple noted that if the firm chose to resubmit the application after the Advisory Committee Meeting, we would try to be prompt in reviewing the conclusions of the Advisory Committee or any additional analyses the firm submitted. The firm said they are inclined to attend the August meeting, but would discuss the matter internally and let Division know as soon as possible.

Summary of Main Action Items

- Dr. Temple said the new analyses submitted by the firm do not alter the Agency's view that the benefit to risk assessment of the drug does not support approval. Therefore, the Agency will likely issue a not approvable letter by July 16, 2001 to meet its regulatory obligations. Nevertheless, the approvability decision is a "close call" and the Agency would like to present the drug to the Cardio-Renal Advisory Committee Meeting in August. The firm said they would discuss the invitation to the Advisory Committee Meeting internally before formally committing to attend the meeting.

- The firm should submit the following 3 items:

  1. Additional demographic data on the symptoms of orthopnea and syncope.
  2. Specific information on how the symptom assessment was made by the physician (via the Case Report Form).
  3. Additional information about pain medication use, including that of opiates. This could include statements from investigators that showed that pain medication use, especially opiates, decreased over time when patients were treated with Remodulin.

  Dr. Temple said that when the new information was submitted, we would review it. He reiterated, however, that he was not optimistic that this new information would change the Agency's current thinking about the approvability of the drug.

Minutes Preparation: /S/
Edward Fromm

Concurrence Chair: /S/
Robert Temple, M.D.

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NNguyen-7-2-01
JLawrence-7-2-01
JHung-7-2-01
AKarkowsky-7-3-01
DThrockmorton-7-3-01

Minutes of a Meeting between United Therapeutics and the FDA

Date: April 11, 2001

Applications: NDA 21-272
Remodulin (treprostinol sodium) Injection

Applicant: United Therapeutics

Subject: Agency Feedback on Approvability of the Drug

FDA Participants:

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Abraham Karkowsky, M.D., Ph.D., HFD-110, Medical Team Leader
James Hung, Ph.D., HFD-110, Statistician/Team Leader
John Lawrence, Ph.D., HFD-110, Statistician
Nhi Nguyen, Pharm.D., HFD-860, Clinical Pharmacology and Biopharmaceutics
Natalia Morgenstern, HFD-110, Chief, Project Management Staff
Daryl Allis, HFD-110, Project Manager
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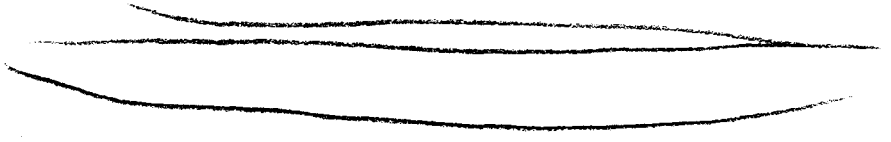
John Guzman, HFD-110, Project Manager
Quynh Nguyen, Pharm.D., HFD-110, Project Manager
Edward Fromm, HFD-110, Project Manager

United Therapeutics

James Crow, Ph.D., President and Chief Scientific Officer
Roger Jeffs, Ph.D., Executive Vice President
Dean Bunce, Director, Regulatory Affairs
Carl Arneson, M.Stat, Manager of Biostatistics and Data Management



Background

Remodulin was submitted as NDA 21-272 on October 16, 2000 for the treatment of pulmonary arterial hypertension (PAH). The drug was granted a priority review with a user fee goal date of April 16, 2001. The sponsor requested a meeting to discuss the Agency's regulatory decision as well as other issues relating to the review of the application.

Meeting

United Therapeutics opened the meeting by presenting a slide that summarized the primary and secondary endpoints of the studies with Remodulin. They also said that a new analysis combining the results of the primary endpoint (6 minute walk test) and a secondary endpoint (Borg Dyspnea Score at the end of the 6 minute walk test) showed a clinically meaningful benefit. Other measures, such as the Dyspnea-fatigue rating and symptom scores also indicated an important effect.

Dr. Temple responded by noting that the Agency had not decided formally on regulatory action for this application. He said, however, that the Agency believes that the data presented to date do not support approval for the following reasons:

- Statistical significance, using pre-specified criteria, was not achieved according to the firm's statistical analysis. Dr. Temple said he did not consider this an insurmountable obstacle, as the results were close to the traditional p-value significance of 0.05 for each trial.
- The magnitude of treatment effect (i.e., increase in exercise distance compared to placebo) was very small.
- Infusion site pain and injection site reactions, in most cases requiring therapy, often narcotics, were present in a sizeable fraction of the patients receiving Remodulin, raising the question of whether there was a net clinical benefit.
- Symptom improvements were small and not credible (with the possible exception of the Borg Dyspnea scale results) because the data were generated in what appears to be a substantially unblinded setting (because of injection site reactions).
- The population chosen for the study may not have been correct; it appears that sicker patients may benefit more from the drug than patients who had higher baseline walking distance values.

Dr. Stockbridge said he was also concerned that patients could be treated for symptoms with Remodulin in lieu of Flolan®, a drug that could potentially reduce mortality in PAH patients.

United Therapeutics and Agency representatives then discussed Dr. Temple's and the Division representative's comments in greater detail.

<u>Six minute walk test and Borg Dyspnea Score</u>

The Borg Dyspnea evaluation was an assessment of how the patients themselves described (to a blinded investigator, not the one caring for the patient) this level of effort (how short of breath they were) after completing the walk test. United Therapeutics argued that focusing only on the distance covered in the 6-minute walk test, without considering the patients perception of effort, as indicated by the Borg scores, understates the true impact of the treatment on the patients exercise ability. It was clear that the assumption that patients walk on the treadmill as far as they can is rebutted by the Borg scores, which show only moderate breathlessness.

Dr. Temple noted that the quantitative improvement in the Borg Score was approximately 1 unit, which did not indicate a very large degree of improvement. The degree of improvement in both symptoms (Borg scale) and distance walked may be more evident in a sicker population (i.e., NYHA class III and IV). This data-derived hypothesis, however, would need to be confirmed in another study with this specific population.

The firm said that they believe other statistical re-analyses of the data, to reflect both walking distance and dyspnea, could add robustness to the Borg/Walk distance integrated data. Dr. Temple encouraged the firm to send those reanalyses to the Division; he noted that if the Division received them prior to the (April 16, 2001) goal date, the Agency would classify that response as a major amendment to the NDA. Consequently, the review clock would be extended by 3 months. Short of the submission of the statistical reanalyses, the Agency would have to issue a

not-approvable letter, which would reflect our current evaluation of the data. United Therapeutics indicated that they would submit the reanalyses to the Division prior to the April 16, 2001 goal date.

Infusion Site Pain

Dr. Temple said he believed that infusion site pain could have led to substantial blinding in the study. The firm argued briefly that pain (as reported by the study patients) was not very different in the two treatment groups, but that contention did not account for the significant difference in use of pain medication in the two groups. Moreover, only 1.7 % of the patients reported site pain as a Serious Adverse Event while receiving the vehicle (placebo) compared with 40% of them receiving the drug. Skin reactions at the injection site were also similar in proportion to those reported for pain at the infusion site. Apart from the effect on blinding, infusion site pain/reactions and the need for a sizeable number of patients to use opioids while on the drug, could negate the apparently modest symptom benefits of the drug.

Use of Remodulin instead of Flolan

United Therapeutics asked whether there is any hesitancy approving Remodulin because of the availability of Flolan, a drug that has a potential mortality benefit in PAH. Dr. Lipicky said that the Division, overall, did not believe that the availability of Flolan was a deterrent to the approval of Remodulin. The side effects of Flolan preclude the use of the drug in many patients. The firm agreed, and said that they were not uncomfortable with Remodulin being indicated as a second-line treatment for patients who failed or could not tolerate Flolan.

Randomized Withdrawal Trial

Dr. Temple said, unless a persuasive argument for benefit can be made with the combined walk distance-Borg Dyspnea statistical reanalyses, the firm would need to consider providing more supportive evidence of efficacy for the drug. He recommended that the firm conduct a randomized withdrawal trial in a subset of the many patients that are currently receiving the drug. It would seem optimal to have the study patients be ones that had low baseline walking distances. The endpoint of the study could be exercise tolerance or some other clinically meaningful endpoint.

United Therapeutics representatives said they were concerned that there could be a rapid deterioration in the patient's clinical condition if they were withdrawn abruptly from the drug. Dr. Temple said if that were a concern, patients could be down titrated in stages to prevent abrupt clinical complications. There would need to be close monitoring for deterioration, but given the apparent modest effect of Remodulin, a very substantial deterioration seemed unlikely.

Another reason the firm was doubtful about the randomized withdrawal trial is that patients are very reluctant to risk going on Flolan because of its side effects. Dr. Temple said he understands the patient's dilemma, but noted that if they do not participate in the study, this drug may disappear. The Agency would consider alternative trial designs but they would have to show a clear difference between the treatment groups.

The firm asked if they could conduct a randomized, withdrawal trial in approximately 100 patients, in which the dose of Remodulin was down titrated to zero; at this point if patients were symptomatic they would be transferred to Flolan therapy. Exercise tolerance would be measured after the down-titration to zero. Dr. Temple said this sounded good and should include sicker, type NYHA III and IV patients, but suggested further discussions with the Division to discuss the specifics of this and other possible withdrawal study options.

United Therapeutics said they would consider the different withdrawal study options but noted that they are not likely to conduct such a trial because of resource issues. They noted that the hospitalization expense for even a small study could be enormous.

Conclusion

Dr. Temple said that because of a very small treatment effect shown between the treatment groups and difficulty interpreting the symptom data to date, the Agency would likely issue a not approvable letter for the application. He said, however, the company could submit reanalyses of the combined walk-distance-Borg Dyspnea data and other data (e.g., infusion pain) to buttress the firm's claim of significant symptom benefit of the drug. Such analyses, if received prior to April 16, 2001, would be classified as a major amendment to the application. Consequently, the review clock would be extended by 3 months.

United Therapeutics indicated that they would submit additional, supportive data to the Division by April 16, 2001. They also said that although they are unlikely to conduct a small, randomized withdrawal trial in patients currently on the drug, they would consider the matter further internally.

Minutes Preparation: /S/
Edward Fromm

Concurrence Chair: /S/
Robert Temple, M.D.

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NStockbridge-4-20-01
DThrockmorton-4-21-01
NMorgenstern-4-23-01
RBehrman-4-30-01

Minutes of a Meeting between United Therapeutics and the FDA

Date: January 25, 2001

Applications: NDA 21-272
Uniprost (treprostinol) Injection

Applicant: United Therapeutics

Subject: Division feedback on review process

FDA Participants:

Raymond Lipicky, M.D., HFD-110, Director, Division of Cardio-Renal Drug Products
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James Hung, Ph.D., HFD-110, Statistician/Team Leader
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Dean Bunce, Director, Regulatory Affairs
Carl Arneson, M.Stat, Manager of Biostatistics and Data Management

Background

Uniprost was submitted as NDA 21-272 on October 16, 2000 for the treatment of pulmonary arterial hypertension. The drug was granted a priority review by the Division and has a user fee goal date of April 16, 2001. The sponsor requested a meeting with the Division to discuss the review of the clinical and pharmacokinetic data for the application to date.

Meeting

Discussion Point #1-The Statistical Significance of the Primary Endpoint

The sponsor noted that the overall combined p value of the two trials was about 0.006 and this did meet the pre-specified significance level of $p<0.01$, although the study did not meet the specified statistical criterion that requires at least one of the two studies to have a p-value<0.049. The sponsor argued that there is still sufficient evidence to conclude that there is a treatment effect with

respect to the primary endpoint and the difference between the specifications in the Analysis Plan and the actual results of the trial is small. They pointed out that both individual studies had significance levels of around 0.06 and thus fulfilled a consistency criterion of the protocol. Dr. Lawrence said there appears to be a small treatment effect but said he is unsure if it is clinically meaningful. Dr. Karkowsky said he did not believe there was an overwhelming treatment effect and said the results (of two trials combined) did not meet the traditional standard of $p<0.00125$.

Discussion Point #2-The Robustness of the Primary Analysis

Dr. Karkowsky said that almost every patient receiving the drug experienced infusion site pain; he said a number of these patients were discontinued off the drug and more of them were being classified as being discontinued due to an adverse event (last observation carried forward) rather than due to clinical deterioration (with a worst rank analysis). He said because of this, an unintentional bias might have been created which influenced the results in favor of the drug. The firm responded by noting the following:

1. 18 patients were discontinued due to adverse events and 12 patients due to clinical deterioration. Of the 12 patients discontinued because of deterioration, 6 were on placebo and 6 on the drug.
2. Even if the 18 patients who discontinued due to an adverse event were assigned worst rank, the direction of treatment effect was favorable to Uniprost, with $p=0.14$.

Dr. Karkowsky said he remained unconvinced that patients were being properly classified when they were discontinued from the study; he noted that a considerable number of patients received the rescue therapy, Flolan, and that Flolan was given because of clinical deterioration. He pointed out that one of the criteria in the protocol for a patient to receive a classification of clinical deterioration was the need for Flolan therapy. The firm disagreed, saying that the majority of patients at entry were Class III and IV NYHA patients and thus eligible for Flolan, which is an approved treatment for this class of patients. They presented a slide showing that patients who deteriorated clinically were placed on Flolan within one day while those patients who discontinued from the study due to an adverse event usually took much longer to receive the drug. The firm hypothesized, however, that infusion site pain could possibly alter exercise tolerance and cause an earlier need for Flolan. Nonetheless, they believed that the investigators were properly blinded and that a majority of patients dropped out of the study due to an adverse event (pain) and not clinical deterioration while on the drug.

United Therapeutics said, in summary, that they believe they met the robustness requirement for the primary endpoint, although not to an absolute worst case analysis. Dr. Karkowsky said, other less conservative analyses showed a marginal effect, at best, for the drug; he noted that he would present several analyses of the data (including worst rank for both AE's and deterioration) in his review.

Pain and unblinding

United Therapeutics said the Division had expressed concern that the occurrence of site reaction/pain could have led to unblinding of the treatment assignment. They noted that patients receiving placebo in the trial that had pain (reaction at the site) attributed it to the drug in 95% of the cases and therefore they believe the blinding of the study remained intact. The firm also presented a slide showing that patients with infusion site/pain did not have a more favorable outcome in the study. Dr. Lipicky asked the sponsor how most patients would describe the infusion site pain. The sponsor said that most would describe the pain as a burning, visceral type pain along

with erythema. Dr. Karkowsky asked the firm if they had classified the infusion site reactions by severity. The firm replied that they had not because it would be difficult to classify as every patient's perception of pain is different; they noted that infusion site pain in the placebo group was not enough to discontinue treatment in that group. They also noted that most patients in the treatment group continued therapy even though they experienced site pain.

Dr. Karkowsky noted that concurrent therapy with NSAID's (non steriodal anti-inflammatory drugs) did not appear to alter the treatment effect.

Discussion point #3-The Magnitude and Clinical Meaningfulness of the Treatment Effect

Dr. Lipicky said that there appears to be a small magnitude of effect of the drug but said the Division is unsure if it is clinically meaningful. The firm agreed that the overall change in the 6 minute walk test appears small compared to placebo (and to the results of the Flolan trial) but said that symptom improvement (e.g., dyspnea, fatigue, chest pain) was demonstrated with Uniprost and they believe this is analogous to an improvement in NYHA functional class. They also noted that patients with Class III and IV NYHA heart disease responded more favorably in the walk test than did patients with a lesser severity of disease.

Dr. Karkowsky asked the firm if they had looked at the effect of opioids on chest pain. The firm said they were unsure but would check back with the Division on this item.

Dr. Karkowsky asked the sponsor if they had collected any information on deaths and hospitalizations. The sponsor said that deaths and hospitalizations were not included in the original protocol analysis because Flolan was available as a rescue treatment and is proven to reduce mortality. Dr. Karkowsky said any information about deaths and hospitalizations should be included in Adverse Event reports sent to the Agency.

Discussion point #4-Tolerance Development

Dr. Lipicky said it appears that increasing doses of the drug are needed over time when patients are on therapy with the drug. The firm said that there is some development of tolerance to the drug but noted that this is common with the prostaglandin class of drugs; they said Flolan exhibited similar characteristics. They also noted that clinical deterioration in this class of patients might contribute to the increasing dose of drug needed over time.

Dr. Lipicky asked the sponsor if the infusion site pain was dose-related. The firm said that the pain was dose-limiting, not dose-related.

Dr. Throckmorton asked the firm how likely were patients opting for continuation of therapy (open label use) after the study was ended. The firm said a majority of the patients (about 189 of 200) elected to continue therapy after the study was concluded.

Discussion point #5-Pharmacokinetic Issues

The sponsor said that it had found a laboratory that can conduct human P450 substrate studies as well as one that could further identify the remaining metabolite of Uniprost. They said they are also in the process of identifying a laboratory that can attempt to elucidate the pharmacological activity of the metabolites of Uniprost. They are not sure all of this data could be submitted to the Division by April 16, 2001 and asked if this data were critical to the approval of the drug. Dr.

Lipicky said the company should try to get the missing data to the Division as soon as possible but said the data was not crucial in making a decision about approving the drug.

Other

Dr. Throckmorton asked the firm when their 120 day safety update would be submitted. The firm said the report should be submitted February 16, 2001 to the Division.

Conclusion

Dr. Lipicky said that the firm had not quite met its primary endpoint on exercise tolerance and therefore the Agency would have to make a "judgement call" based on the data from the 6-minute walk test, potential symptomatic benefit (e.g., dyspnea, fatigue, chest pain) from the drug, and other factors such as infusion site pain in the study population. He encouraged continued dialogue between the sponsor and the Division reviewers to iron out minor differences in the study data. Dr. Lipicky said another face-to-face meeting would probably not be productive, although he is open to having one if the sponsor so desires.

Minutes Preparation: /S/

Edward Fromm

Concurrence Chair: /S/

Raymond Lipicky, M.D.

ef/01-31-01/2-06-01

Rd: NNguyen-1-31-01
JLawrence-1-31-01
JHung-1-31-01
AKarkowsky-2-01-01
NStockbridge-2-02-01
DThrockmorton-2-05-01

Minutes of a Meeting between United Therapeutics and the FDA

Date: December 8, 2000

Applications: NDA 21-272
Uniprost (treprostinol) Injection

Applicant: United Therapeutics

Subject: Planning meeting for Cardio-Renal Drugs Advisory Committee Meeting

FDA Participants:

Raymond Lipicky, M.D., HFD-110, Division Director (via telephone)
Douglas Throckmorton, M.D., HFD-110, Deputy Division Director
Norman Stockbridge, M.D., Ph.D., HFD-110, Medical Team Leader
Abraham Karkowsky, M.D., Ph.D., HFD-110, Medical Team Leader
Kooros Majoob, Ph.D., HFD-710, Statistician
Xavier Joseph, DVM., HFD-110, Pharmacologist
Patrick Marroum, Ph.D., HFD-860, Clinical Pharmacology and Biopharmaceutics, Team Leader
Nhi Nguyen, Pharm.D., HFD-860, Clinical Pharmacology and Biopharmaceutics
Jorge Rios, M.D., HFD-45, Division of Scientific Investigations
Natalia Morgenstern, HFD-110, Chief, Project Management Staff
Edward Fromm, HFD-110, Regulatory Health Project Manager
Qunyh Nguyen, Pharm.D., HFD-110, Regulatory Health Project Manager

United Therapeutics

Roger Jeffs, Ph.D., Director, Research, Development and Medical
David Mottola, Ph.D., Director of Clinical and Scientific Affairs
Shelmer Blackburn, Director of Operations
Dean Bunce, Associate Director, Regulatory Affairs
Carl Arneson, Statistician

Background

Uniprost was submitted as NDA 21-272 on October 16, 2000 for the treatment of pulmonary arterial hypertension. The drug is planned for discussion at a February 9, 2001 Cardiac and Renal Drugs Advisory Committee Meeting. United Therapeutics requested a meeting with the Division to discuss planning for the Advisory Committee meeting as well as the status of FDA's review of the product to date.

Meeting

Advisory Committee

Dr. Lipicky opened the meeting by stating that Uniprost was scheduled to be discussed at a February 9, 2001 Cardiac and Renal Drugs Advisory Committee Meeting. He then explained some of the steps of planning for the meeting:

Dr. Lipicky said, that after being briefed by some of the reviewers of the NDA, he thought it was questionable whether the drug would be approved by the Agency. He therefore thought that it would be in the sponsor's and Division's best interest not to discuss Uniprost at the February 2001 Advisory Committee Meeting. Dr. Lipicky said that the Division would likely give an unfavorable recommendation of the product to the Committee; he also believed that the issues involved with the drug would not lend themselves to a useful meeting. Dr. Lipicky noted that the chances of Uniprost getting an unfavorable rating by Dr. Temple (who will decide whether to approve the drug) would be increased by unfavorable reviews both by the Division and potentially the Advisory Committee.

Dr. Lipicky said that it may be possible to move the Advisory Committee meeting to March 2001 in order to give the sponsor and Division more time to discuss the studies and issues presented at the meeting today. He said that if the sponsor does not want to go to the Advisory Committee the Division would be available for future telecons or face-to-face meetings to discuss the results of the studies. United Therapeutics said that they would give serious consideration to the Division's comments and will let the Division know early next week whether they want to attend the February or March 2001 Advisory Committee meeting.

Dr. Lipicky said that there were several issues regarding efficacy of the drug that cast uncertainty on approval of the drug. They are:

- Two exercise trials that involved walking distance showed point estimates that leans in favor of the drug, but not with p values<0.05. Dr. Lipicky said that two trials together should yield a p value in the range of p<0.00125. He noted that the point estimate of the two trials showed only a few percent greater difference than baseline which is not a striking magnitude of effect. Dr. Lipicky said that overall the Division thinks that the drug may offer some symptomatic benefit, but cannot at this time, confirm with certainty the sponsors claim of efficacy of the product. He noted, however, that the drug is being proposed for use in an orphan population and that the drug offers potentially improved convenience over Flolan; he

said these factors are important and will be given consideration in the evaluation of the product.

- There has not been enough data submitted by the sponsor to determine if the drug has a positive effect on morbidity and/or mortality.
- There is concern that tolerance develops with the drug, as evidenced by progressive increases in dose.

Primary Medical Reviewer's Comments

Dr. Karkowsky said that he had the following comments about the studies he has reviewed to date:

- There were patients who were discontinued from the drug due to infusion site pain; he said that the blinding of the study might be compromised if these patients are not adequately accounted for. Dr. Karkowsky said there are several ways of analyzing these patients; one way would be to do a LOCF (last observation carried forward) analysis for all patients even for those who died or received transplants; he said it appears that the drug has a p value of >0.01 in the pooled studies and a lesser effect in the other studies.
- Quality of life data appear to lean in the right direction but Dr. Karkowsky said he was unsure of the assessment data due to patient dropouts and potential unblinding in the studies.
- There appears to be no net increase or decrease for other medications during the studies.
- There appears to be a small positive effect on hemodynamics (e.g., pulmonary wedge pressure).

Safety

Dr. Stockbridge, the medical officer who is doing the integrated safety review of the studies for Uniprost said, that at the present time, the safety information provided by the company appears to be adequate.

Dr. Throckmorton asked if the P:06 trial (open label) was still ongoing and when the Safety Update would be coming to the Division. The sponsor said that the P:06 trial was still ongoing and that data from that trial (through October 1, 2000) will be included in the Safety Update, scheduled to be sent to the Division in mid-February 2001.

Biopharmaceutics review

Dr. Nguyen said that there appeared to be 5 metabolites of the drug whose activity has not been characterized. She said she was concerned about possible long-acting metabolites that may accumulate; the radio-labeled study showed a plasma half-life of 65 hours versus a blood half-life of 2 hours. The firm said that they know that no one metabolite is greater than 15 % of the dose but are not sure of the activity of the metabolites at the present time.

Dr. Marroum asked the company if Uniprost was metabolized by CYP450 enzymes. The firm said that it does not seem to inhibit CYP450. The drug did not induce CYP450 in rats. (Note: after the meeting the firm indicated to Dr. Nguyen that they would determine if Uniprost is a substrate for CYP450).

United Therapeutics asked if there was modeling done to look at the hemodynamic effects of the drug. Dr. Marroum said that there has been no modeling done to date but that Dr. Gobburu will do

modeling to look, for example, at the relationship between dose and possible tolerance development.

Statistical review and dose escalation

Dr. Throckmorton said the statistical reviewer, Dr. Lawrence was unable to attend, but said his impression of the data was that the analysis done by the sponsor yielded the most robust result possible and that the marginal effect of the drug were not be improved by any of the further reanalyzes by the Division. The sponsor noted that they had difficulty quantifying the effect because some patients were too ill to exercise. They said they used a Kaplan-Meyer analysis to try to account for this and found about a 10% difference between groups when using this method. Dr. Lipicky said that there might be a treatment effect but it appears to be very small. He also expressed concern that the drug was not being dosed correctly or perhaps tolerance was developing. Dr. Lipicky said these issues would be difficult to address after approval of the drug. The firm replied that the 10-20 fold increase in dose was similar to Flolan and noted that there was need for a dose increase with Flolan even after approval. They noted that data from the P:06 trial were supportive of their belief that the rate of dose escalation appears to plateau. Dr. Throckmorton said the Division had looked at published data on dose escalation with Flolan that suggested that the increases in dose were smaller with Flolan than Uniprost. The company said that there was probably some tolerance with Flolan but that the literature shows that the drug is still effective. They added that they believed that because Uniprost would be given by subcutaneous injection that it would serve a wider population than Flolan and one that was not as sick as Flolan's.

Other

Dr. Throckmorton said that it appears that in the P:04 and P:05 study that 10-15% of patients had two or three identical walk distances. The firm said they would sort out the confusion in the datasets.

Conclusion

Dr. Lipicky said, at the present time, it was questionable whether the drug would be approved by the Agency. He therefore thought that it would be in the sponsor's and Division's best interest not to discuss Uniprost at the February 2001 Advisory Committee Meeting. He said, however, the decision to attend was up to the sponsor and that he would try to see if a March date is available to give the sponsor and Division more time to resolve differences in the data submitted to the Division. The firm said they would consider the comments by the Division and would let the Division know whether they still wanted to attend the Advisory Committee meeting.

Minutes Preparation: /S/
Edward Fromm

Concurrence Chair: /S/
Raymond Lipicky, M.D.

ef/12-19-00/1-02-01

Rd: QNguyen-12-12-00
NNguyen-12-20-00

PMarroum-12-20-00
KMajoob-12-20-00
AKarkowsky-12-21-00
NStockbridge-12-21-00
DThrockmorton-1-02-01

Minutes of a Meeting between United Therapeutics and the FDA

Date: December 7, 2000

Applications: NDA 21-272
Uniprost (treprostinol) Injection

Applicant: United Therapeutics

Subject: CMC issues with NDA application

FDA Participants:

John Simmons, Ph.D., Director, Division of New Drug Chemistry I (HFD-810)
Kasturi Srinivasachar, Ph.D., Team Leader, Division of New Drug Chemistry I (HFD-810)
J.V. Advani, Ph.D., Review Chemist, Division of New Drug Chemistry (HFD-810)
Edward Fromm, HFD-110, Consumer Safety Officer
Qunyh Nguyen, HFD-110, Consumer Safety Officer

United Therapeutics

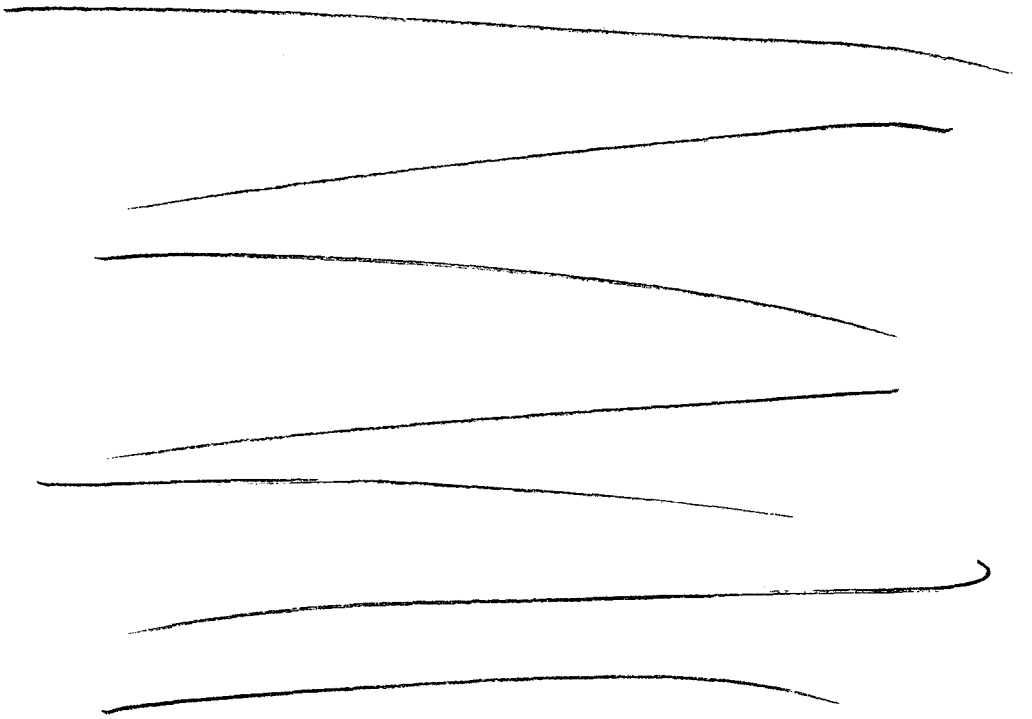
Dean Bunce, Director, Regulatory Affairs
David Walsh, Ph.D., Executive Vice President and Chief Operating Officer, Production

Background

Uniprost (treprostinol) Injection was submitted as a NDA on October 16, 2000 and given a priority review by the Division. The Division requested a meeting with the sponsor to discuss CMC questions it had with the synthesis of the drug substance.

Meeting

Dr. Simmons opened the meeting by stating the Agency was concerned that numerous steps in the synthesis of the drug substance were not under GMP control. He said the Agency was especially concerned with controls and cross contaminants that may not be accounted for in the earlier steps of synthesis of the drug substance. Dr. Simmons said that the Agency would have to have the entire sequence of steps used in the synthesis of the drug substance under GMP control until enough experience is obtained from the company to justify relaxing those controls or outsourcing intermediates. The firm said that it has defined [redacted] as the starting material at which strict adherence to GMPs and Process Validation are initiated. They said that the [redacted]



Impurities

Dr. Srinivasachar noted that the firm listed impurities for [redacted] by relative retention time and asked if the company has elucidated the structure of these compounds. The firm said they have limited information obtained by [redacted] that indicates that some of the impurities are [redacted]

Dr. Advani noted that each impurity identified in the toxicological batch data would need to be associated with preclinical or IND studies. The firm replied that that information could be found in Volume 1.6 of the NDA submission. Dr. [redacted]

Dr. Advani questioned why [redacted] impurities, [redacted] have a [redacted] acceptance criteria, whereas all other impurities were [redacted] Dr. Srinivasachar said that the firm should look at current manufacturing batch data and tighten this limit, if appropriate. In general, specification limits should be based on current manufacturing and analytical capabilities and not on early developmental batches.

Stability Data

Dr. Advani said that the Division was still awaiting stability data for the 10 mg dosage strength. The company said that they would send that data into the Division soon.

Identification test