

Dr. Srinivasachar said a _____ identification test should be added to drug product specifications. Dr. Simmons encouraged the firm to send any specific rotation data they have into the Division for review.

Carton Labels

Dr. Advani said carton labels are needed for all four strengths of Uniprost. The firm said they would supply these as artwork if that were acceptable to the Division. Dr. Advani said it was acceptable.

How Supplied section

Dr. Advani noted that the HOW SUPPLIED section of the draft labeling was incomplete (i.e., it did not include the storage statement and other information). The firm said they had inadvertently left out that information and would submit draft labeling correcting that omission.

Conclusion

Dr. Simmons expressed concern that the _____ of the manufacturing process of drug substance were not covered by GMP guidelines. He said that the Division would contact the Office of Compliance, to review in detail, the completed FDA inspection of the manufacturing facility. He said that the Agency would set up a telecon with the sponsor to discuss the FDA inspection as well as other issues needing clarification pursuant to the meeting with the sponsor.

Minutes Preparation: /S/ —
Edward Fromm

Concurrence Chair: /S/
John Simmons, Ph.D.

ef/12-11-00/12-14-00/01-05-01

Rd: NNguyen-12/12/00
 JVAdvani-12/13/00
 Ksrinivasachar-12/13/00

cc: NDA 21-272
 HFD-110
 HFD-110/EFromm/SMatthews

Minutes of a Meeting between United Therapeutics and the FDA

Date: November 15, 1999

Applications:
UT-15 Injection

Applicant: United Therapeutics

Subject: Pre-NDA Meeting

FDA Participants:

Robert R. Fenichel, M.D., Ph.D., HFD-110, Deputy Division Director
Douglas Throckmorton, M.D., HFD-110, Medical Officer
James Hung, Ph.D., HFD-110, Statistician/Team Leader
Xavier Joseph, DVM., HFD-110, Pharmacologist
Nhi Nguyen, Pharm.D., HFD-860, Clinical Pharmacology and Biopharmaceutics
Khin Maung U, M.D., Ph.D., Division of Scientific Investigations
Karen Storms, HFD-45, Consumer Safety Officer, Division of Scientific Investigations
Natalia Morgenstern, HFD-110, Chief, Project Management Staff (pre-meeting only)
Edward Fromm, HFD-110, Consumer Safety Officer

United Therapeutics

James Crow, Ph.D., President and Chief Scientific Officer
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

Consultants

Background

UT-15, a chemically stable tricyclic benzindene analog of epoprostenol (prostacyclin), possesses potent pulmonary and systemic vasodilatory and platelet anti-aggregatory actions in vitro and in vivo. The ability of UT-15 to reduce the loading condition of the right ventricle suggests that this agent may have utility in the treatment of pulmonary hypertension. The acute hemodynamic profile of UT-15 in patients with pulmonary hypertension appears similar to that of epoprostenol (Flolan), which is approved to treat pulmonary hypertension. Unlike epoprostenol, however, which must be delivered by continuous intravenous infusion, UT-15 has sufficient chemical stability to allow for subcutaneous administration, offering patients and clinicians an alternative therapeutic route of administration.

UT-15 was designated an orphan drug for the indication of Pulmonary Arterial Hypertension (PAH), effective November 2, 1999. The firm plans to submit an NDA for UT-15 in June 2000 and is requesting the Division's feedback on the format and content of the proposed package.

Meeting

The firm opened the meeting by giving a brief background of pulmonary hypertension (PH). The firm noted that they are now requesting a change in designation of pulmonary hypertension to pulmonary arterial hypertension (PAH), per the September 1998 World Symposium on Primary Pulmonary Hypertension. They added that they were primarily concerned with the vascular forms of PH, both primary (PPH) and secondary. United Therapeutics noted that about 3000 patients per year were diagnosed with (PPH), and about 3 times that amount for secondary forms of pulmonary hypertension.

Carcinogenicity/Toxicology Studies

The firm said that they had completed 6 month toxicology studies in rats and dogs but have not done carcinogenicity studies. Citing technical problems with the 6 month rat study, they stated that standard two year rodent studies for evaluation of carcinogenic potential could not be done because of the increased mortality that would be expected with the required duration of continuous infusion. Dr. Throckmorton asked about the feasibility of doing a shorter term alternative assay for determining carcinogenic potential. The sponsor noted that such alternative assays, which are generally performed in mice, were not feasible due to the difficulty of continuously infusing such a small animal for 6 months or longer. Dr. Fenichel stated that carcinogenicity studies might not be feasible or necessary now but that if the Carcinogenicity Assessment Committee (CAC) requests that the studies be done then the sponsor would have to begin these studies prior to filing the NDA. He indicated that the sponsor should submit additional information to the Division supporting its view that carcinogenicity studies are not necessary for this drug. These should include data on the mortality of patients with secondary forms of pulmonary hypertension.

Pharmacokinetics

Dr. Joseph asked the firm if there was any data on protein binding. The firm said that it has not been able to determine the protein binding of UT-15 because UT-15 is an extremely potent drug and because the C-14 label UT-15 synthesized had so much radioactivity that it was unstable (i.e., self-degraded) even at -70 degrees C. Dr. Nguyen asked the firm if there were difficulties conducting the C-14 mass balance study due to the instability of the radiolabeled UT-15. The firm said that it will remount the C-14 study in December. All events will be synchronized to reduce the time the C-14 compound is stored, i.e., the preparation and sterilization of the C-14 UT-15 Injection, the start of the clinical phase (including obtaining IRB and radiation safety committee approval), and the analysis of various biological fluids. The excretion of radioactivity via both the biliary route and the renal route will be measured. Metabolites in the urine will also be examined. However, until the experiment is completed, it is unknown whether the metabolites have or have not been degraded due to the large amount of radioactivity in the C-14 labeled compound.

Dr. Nguyen asked if the firm had done pK analyses of the studies. The firm said that in P01:04 and P01:05, steady-state plasma samples were collected from individual patients during the weeks 6 and 12 visits, at which time clinical assessments were also made. The plasma clearance levels will be determined from the steady-state plasma concentration (and UT-15 dose). The multivariate analysis will investigate whether various patient factors (i.e., demographics and concomitant medications)

would explain some of the variability in UT-15 plasma clearance values. Dr. Nguyen indicated that this was acceptable.

Dr. Nguyen inquired whether there had been an analysis of drug-drug interactions. The firm said limited studies have been done.

Safety/Efficacy

Dr. Throckmorton inquired how many patients United Therapeutics would have at the time of filing of the NDA. The firm indicated that they will have 301 patients treated for the Efficacy population and is expecting an approximate total of 852 volunteers and patients exposed for the Safety population. Dr. Throckmorton thought it would be beneficial to use confidence intervals when analyzing the mortality data. The firm said that it could calculate confidence intervals for relative risk ratio and risk difference for mortality and transplantation in the randomized, placebo controlled studies. Dr. Fenichel noted that the confidence intervals could have broad limits if needed.

Dr. Fenichel said, if feasible, the firm should follow patient failures (e.g., those that went to Flolan) through the 12 week endpoint, to gather a combined endpoint of mortality, lung transplantation, and switch of therapy.

Dr. Throckmorton noted that outlier analyses of safety parameters (e.g., ALT, AST) would be important with this drug. He said shift tables would be helpful in analyzing the safety information. Dr. Fenichel remarked that the small numbers of patients in the studies are conducive to using data-graphical displays to identify outliers.

Dr. Throckmorton asked the firm if the ECG's were abnormal in the patients studied. The firm said in the context of shifts from "normal to abnormal" or "abnormal to a different type of abnormal" ECG, they did not notice anything significant. They also mentioned that they had not studied QT interval changes.

Dr. Fenichel commented that approval guidelines contain three essential elements; that the drug is safe, is effective, and has reasonable instructions for use. He noted that there were no instructions for physicians on how to discontinue the drug. He was particularly concerned about rebound pulmonary hypertension as this event was associated with Flolan. The firm responded by saying that at least one subject died after withdrawal, but that the death occurred about 48 hours later and therefore did not appear to be attributable to a rebound worsening of pulmonary hypertension. United Therapeutics also noted that the half-life of Flolan was about 2 minutes whereas UT-15 had a much longer half-life. The firm was encouraged to include a discussion of 'rebound' in their NDA.

Statistical

Dr. Fenichel inquired about the analyses of PAH and the subset analysis of PAH and whether the firm needed to accept a penalty for the two analyses. The firm explained that the primary analysis is a combined analysis of all patients in studies P01:04 and P01:05. If the combined analysis is significant (two-sided $p < 0.049$), that will serve as justification to look at each study separately. If each protocol has two-sided $p < 0.049$, this would be considered acceptable. If one study is $p < 0.049$ and one study is $p > 0.049$, then United Therapeutics will go back to the combined analysis to determine if it is clearly and robustly below $p < 0.01$. If combined study analysis is $p \leq 0.01$, this will be considered acceptable. If not, then the firm will look at the subset for PPH for significance (two-sided $p < 0.001$). Dr. Fenichel indicated that this approach did not need to have any penalties of the different types of analyses.

The firm indicated that they would submit a detailed statistical plan to the Division towards the end of January 2000. They said that a data lock would be set for the end of March and asked if the Division could review the plan and provide feedback to the firm by the end of February. Dr. Hung said he would be able to this.

Format

The Division indicated that the following items should be submitted in electronic format:

- Annotated Case Report Forms (SAS files with SAS variables)
- Integrated Safety and Efficacy
- Key pK studies
- draft labeling (4 or 5 copies on floppy disks)
- SAS data sets from clinical studies

The firm asked if Word 2000 documents were compatible with the Division's computers. Dr. Fenichel said that the Division used Word 97 now, but that Word 2000 was coming in, and that in any event this wouldn't be a problem, since Word 2000 can save files in Word 97 format.

Mr. Fromm asked the firm to include a pediatric section (i.e., how they plan to respond to the pediatric rule) in the NDA package.

Conclusion

The firm plans to submit this NDA in June of 2000. The firm plans on submitting a detailed statistical plan in January and the Division has promised a review of the plan by the end of February.

Addendum

Dr. Nguyen noted that with regard to protein binding, the sponsor could determine protein binding by an in-vitro methodology that does not require a radiolabel.

Minutes Preparation:

/S/
Edward Fromm

Concurrence Chair:

/S/
Robert R. Fenichel, M.D., Ph.D.

ef/11-17-99/11-26-99/12-6-99

Rd: KMaug U/11-19-99
DThrockmorton/11-29-99
XJoseph/12-1-99
NNguyen/12-1-99
JHung/12-3-99

cc:

HFD-110

HFD-110/EFromm/SMatthews

Minutes of a Meeting between United Therapeutics and the FDA

Date: November 8, 1999

Applications:
UT-15 Injection

Applicant: United Therapeutics

Subject: Pre-NDA Meeting (CMC)

FDA Participants:

Hasmukh Patel, Ph.D., Acting Deputy Director, Chemistry, Division of New Drug Chemistry I (HFD-810)
Kasturi Srinivasachar, Ph.D., Team Leader, Chemistry, Division of New Drug Chemistry I (HFD-810)
Joseph Piechocki, Ph.D., HFD-810, Chemist
Edward Fromm, HFD-110, Consumer Safety Officer

United Therapeutics

James Crow, Ph.D., President and Chief Scientific Officer
David Mottola, Ph.D., Director of Clinical and Scientific Affairs
Shelmer Blackburn, Director of Operations
Dean Bunce, Associate Director, Regulatory Affairs

Background

UT-15 Injection is a chemically stable tricyclic benzindene analogue of prostacyclin (PGL₂) with potent pulmonary and systemic vasodilatory and platelet anti-aggregatory actions in vitro and in vivo. Unlike Flolan (epoprostenol), which must be delivered by continuous intravenous infusion, UT-15 has sufficient chemical stability to allow for subcutaneous administration, offering patients and clinicians an alternative therapeutic route of administration. United Therapeutics plans to submit this NDA in the second quarter of the year 2000 and is requesting the Division's feedback on the format and content of the CMC section of the proposed package.

Meeting

Table of Contents

- 1) (Manufacturer of Drug Substance) Dr. Piechocki asked that CFN numbers be obtained for all manufacturers that are working on this project.

- 2) (Drug Substance Controls-Rationale for Specifications and Limits) Dr. Srinivasachar noted that it was important to look at each impurity and qualify it.
- 3) (Method of Manufacture-Description of Process (Master Production Records) The firm indicated that they would include a sample for each strength.
- 4) (Container-Closure System) The firm agreed to provide data to demonstrate suitability of the container-closure system to be used for the marketed drug product as per Dr. Patel's request. It will include data on extractables from the container-closure system. Dr. Piechocki noted that a description of the _____ process used for the stoppers be included in the Container-Closure and Sterilization Process Validation sections of the NDA. The stoppers are _____ after washing.
- 5) (Stability of Drug Product-Stability Commitment and Expiration Date Statement) Dr. Piechocki said the Division needs executed batch records.
- 6) (Labeling) Dr. Patel noted that the carton label was also needed.
- 7) (Drug Substance Reference Standard) The company was informed that submission of only COA for the reference standard is not adequate. Information on its synthesis, purification, and characterization should also be provided.
- 8) (Batch Analysis Tables) Dr. Srinivasachar thought Investigational Formulations would be a more appropriate title for this section.
- 9) (Environmental Assessment) Dr. Piechocki asked that the firm to send in a separate request for the environmental assessment exemption.
- 10) (Sterilization Process Validation) Dr. Piechocki asked the firm to send this section in a separate jacket because microbiologists in another area review this section.

Stability Assessment Section

Dr. Piechocki noted that the stability data has positive slopes, which may indicate a packaging problem.

Bracketing of primary studies for the 1.0 mg/ml, 2.5 mg/ml, and 5.0 mg/ml strengths is acceptable. Bracketing will include:

_____ Primary stability batches were manufactured according to the proposed commercial process and packaged in the proposed container-closure system. Dr. Patel noted that shelf life expiration would be based on supportive and primary stability batches submitted in the NDA package.

According to the sponsor, the stability protocol submitted in the meeting was based on the recommendations from the Division received by them in the last meeting. The protocol discussed at that time included the 10 mg strength. The batches indicated in the stability protocol proposed in this meeting package have already been placed on stability. As it was previously agreed, the Division accepted the proposed stability protocol.

Dr. Patel asked the firm to do _____ of primary stability studies with the 10 mg/ml formulation. The firm said that they would have difficulty doing this because their clinical trials have not needed this strength yet. They noted that they have _____ stability data for _____ and _____ data on another batch. Because of this, the original NDA will include data supporting a _____ expiration date. Dr. Patel said _____ of primary stability data for the 10 mg/ml formulation were sufficient for now as it was agreed at the last meeting but asked the firm to send the _____ batch in when data is available. The firm indicated that additional 10 mg/ml stability data from the NDA batches will be filed to the NDA as an amendment during the review cycle. The stability data from a _____ 10 mg/ml batch will be submitted in an Annual Report to the NDA when available. It

was agreed that amending the NDA for the additional stability data would not restart the review clock. However, the data may not be reviewed if submitted too late during the review process.

Dr. Patel stated that the bacterial endotoxin test should be added to the stability protocol at the end-of-shelf-life for designated batches of each strength (1, 2.5, 5 and 10 mg/ml). Dr. Srinivasachar asked why metacresol was used as a preservative. The firm said that metacresol was a microbial preservative and noted it was used in insulin pumps. Dr. Piechocki said he was concerned about degradation of metacresol and recommended that the firm do the Preservative Effectiveness Test at the last station of all stability test protocols.

Photostability Section

Dr. Srinivasachar asked if there were any formulation differences between the _____ glass. The firm replied that there were no differences and mentioned also that the _____ glass was easily obtained.

Use of _____ glass for the commercial product is acceptable if data to demonstrate its suitability for the drug product and stability of the drug product are provided. The shelf life will be based on the quantity and quality of the data submitted for the _____ glass vials. Supportive data may be used to determine the shelf life.

Dr. Piechocki noted that the firm would need to justify the spectral power distribution of their UV lamps. He also stated that when doing forced degradation studies with light and heat that the degradation products need to be identified (per ICH guidelines) as to whether they resulted from heat or light or both.

Impurities

Dr. Srinivasachar asked what _____ tests they had done with the drug product. The firm said they would use _____ to test for _____. Dr. Srinivasachar urged the firm to do a specific _____ test for the drug product. He added they would have to show justification if they decide not to do the test.

Dr. Piechocki requested that the pH specification be tightened from 6.5 ± 1.0 to 6.5 ± 0.5 . The analytical data will be examined to determine the final specification to be submitted in the NDA.

Dr. Piechocki noted that the melting point range was a little wide.

Proposed Drug Substance Specifications

Dr. Srinivasachar stated that only one limit for Total Impurities was needed. Total Unidentified Impurities should be included within Total Related Substances. Dr. Srinivasachar noted that Total Volatiles could be deleted due to the assay being redundant with Water and Residual solvents.

Conclusion

The firm said that they plan to submit the NDA in June of 2000. They have agreed to send in stability information for the 10 mg/ml formulation as it becomes available.

Minutes Preparation:

/S/
Edward Fromm

Concurrence Chair:

/S/
Hasmukh Patel, Ph.D.

ef/11-19-99/11-24-99/12-8-99

Rd: JPiechocki/11-23-99
KSrinivasachar/11-23-99

cc:
HFD-110
HFD-110/EFromm/SMatthews

MEETING MINUTES

MAR 11 1998

Date: February 20, 1998

Subj: UT-15 (formerly 15AU81) for pulmonary hypertension
End of Phase 2 Meeting

Sponsor: United Therapeutics (formerly Lung Rx)

Meeting Chair: Robert Temple, M.D.
Sponsor Lead: James Crow, Ph.D.
Recorder: Gary Buehler

Attending:

United Therapeutics

James Crow, Ph.D.

Shelmer Blackburn

President

Project Leader

FDA

Robert Temple, M.D.

Raymond Lipicky, M.D.

Shaw Chen, M.D., Ph.D.

Douglas Throckmorton, M.D.

Xavier Joseph, DVM

Kooros Mahjoob, Ph.D.

Gary Buehler

Director, ODE I, HFD-101

Dir., Div. of Cardio-Renal Drug Prod., HFD-110

Medical Group Leader, HFD-110

Medical Reviewer, HFD-110

Pharmacology Reviewer, HFD-110

Statistical Reviewer, HFD-710

Project Manager, HFD-110

BACKGROUND

UT-15, a chemically stable tricyclic benzindene analog of epoprostenol (prostacyclin), possesses potent pulmonary and systemic vasodilatory and platelet anti-aggregatory actions in vitro and in vivo. The ability of UT-15 to reduce the loading condition of the right ventricle suggests that this agent may have utility in the treatment of pulmonary hypertension. The acute hemodynamic profile of UT-15 in patients with pulmonary hypertension is similar to that of epoprostenol (Flolan); both drugs increase cardiac output and decrease pulmonary artery pressure and pulmonary vascular resistance. Unlike epoprostenol, however, which must be delivered by continuous intravenous infusion, UT-15 has sufficient chemical stability to allow for subcutaneous administration, offering patients and clinicians an alternative therapeutic option.

UT-15 was originally developed by the Burroughs Wellcome Co. as 15AU81 for CHF.

Sponsorship of the IND was transferred to Lung Rx on February 10, 1997. Lung Rx changed the name of the compound from 15AU81 to LRX-15. Lung Rx subsequently changed their name to United Therapeutics and changed the name of the compound to UT-15.

DISCUSSION

Pharmacology

The firm was informed that if they completed the standard mutagenicity tests on the drug, it is highly probable that the Carcinogenicity Assessment Committee (CAC) would agree that carcinogenicity studies would not be required for the approval of this drug. If the CAC does agree, the studies proposed in the pre-meeting package would be acceptable.

The firm stated that they have completed a 90 day continuous subcutaneous infusion study in rats, and a similar study in dogs is planned. They propose to do a 6 month study of similar design in rats, but they are concerned about being able to complete it because of the difficulty in administering the drug SC for that period of time. They were informed that the NDA would not be refused to file if they are not able to complete the study. They need, however, to attempt the trial.

Number of Endpoints

After establishing that the firm hopes that primary pulmonary hypertension patients (PPH) will make up about 1/3 of the total recruitment for their trial, the suggestion was made to consider two primary endpoints, one for the total enrollment and the second for PPH patients. Given only two endpoints, one of which is included in the other, it was estimated that the statistical penalty for doing this would result in testing both endpoints at the 0.035 level of significance. A second suggestion was to look at the two groups (PPH patients and non-PPH patients) separately, especially if the thought is that non-PPH patients may not respond as well. The correction in this case probably would be greater because the two endpoints (subsets) are completely independent. The alternative, to plan on analyzing all patients and going on to the subset and having only one achieve significance without clear rules would be potentially troublesome.

The firm asked what decision would result if the p value for the entire study was less than 0.035, but the PH subgroup was significant at 0.035. The Agency responded that if there was not a lean in the right direction for the other patients, the indication would probably be narrowed to only PH patients. If there was a lean, it would require a judgment.

Involving Other Sponsors

The firm was approached about meeting with other sponsors who are studying PH. Because these patients are so rare, and the various proposed therapies, using different mechanisms of action, would be competing for these patients, it was thought that some type of joint effort could be attempted. Also, the possibility of finding that a combination of therapies was more effective than any of the single entities would offer a significant benefit to the PH patients.

The firm stated that they were a small company with limited resources. While they would probably not object to discussing a proposal, they would not want to have to delay their

development program as a result of a cooperative effort.

NOTE: The firm called a few days after the meeting and agreed to discuss the above approach with other sponsors.

Choice of Endpoint

The firm was informed that the six minute walk test was an acceptable primary efficacy variable. The problem with it, however, is that it is not as convincing as a morbidity/mortality endpoint. The firm was encouraged to collect long-term data to determine if the therapy affects the overall morbidity and mortality of the patients. Hospitalizations, need for Fiolan, transplantation or decompensation would all be acceptable markers of morbidity. It was suggested that the results could be compared with outcome data compiled by NIH on PPH patients before and after the availability of Fiolan. The firm said that they could do this, but they thought that they would only be able to do the comparison in PPH patients since comparative data do not exist for the non-PPH patients.

Tolerance

The firm was encouraged to investigate whether the need to adjust the dose upwards on the basis of need is a signal that tolerance is developing or simply a progression of the disease process. The firm said there appears to be a difference in the acute tolerance to the drug in normals vs. PPH patients. They therefore thought that animal models would be of limited use. It was suggested that they compare a dose that seems to be higher than is needed to their established top dose to determine if long-term outcome improves.

End of Therapy

The firm explained that once a patient is started on therapy, it is very dangerous to abruptly discontinue the drug. They therefore requested that investigators be able to unmask the blind for the study when the 12 week double-blind period is over to safely continue the patients on appropriate therapy. This was perceived as a potential problem by Agency reviewers. To decrease the possibility that the investigators will know what patients are on active drug, it was suggested that the investigator not have access to the exercise or other efficacy data in the chart. All efforts should be made to preserve the blinding of the trial.

Interim Looks

The proposal for interim looks (3 for safety and 1 for efficacy) outlined in the pre-meeting package was considered acceptable.

DECISIONS

1. The proposal for not doing carcinogenicity testing for this drug and indication would be presented to the CAC for their decision.
2. The firm was encouraged to include separate primary endpoints for either all patients and PPH patients or PPH patients and non-PPH patients.

3. The firm will notify the Division if they would be willing to meet with other sponsors pursuing the pulmonary hypertension indication.
4. The firm will attempt to compare the long-term outcomes from their trial with the historical data compiled by NIH on patients with PPH. They will not be able to do the comparison with non-PPH patients.
5. The firm was encouraged to investigate, through animal studies or in their clinical trials, if tolerance is developed to UT-15.
6. The firm was cautioned that all attempts should be made to preserve the blinding of their trial if it becomes necessary to unmask the treatment for each patient at the end of the 12 week trial period to determine the follow-on therapy.
7. The method proposed by Dr. Koch for interim looks for safety and efficacy was acceptable.

Minutes prepared by: /S/

Gary Buehler

Concurrence, Chair: /S/

Robert Temple, M.D.

Orig IND

HFD-110

HFD-110 GBuehler

HFD-110 SBenton

RD:	KMahjoob	2/23/98
	DThrockmorton	2/23/98
	SChen	2/23/98
	XJoseph	2/24/98
	RTemple	3/3/98

Minutes of a NDA Filing Meeting

Date: November 3, 2000

Application: NDA 21-272
Uniprost (treprostinol sodium) Injection
1.0, 2.5, 5.0, and 10mg/ml

Type: 1P

Applicant: United Therapeutics Corporation

User Fee Goal Date: April 16, 2001

Participants:

Raymond Lipicky, M.D., HFD-110, Director, Division of Cardio-Renal Drug Products
Norman Stockbridge, M.D., Ph.D., HFD-110, Medical Team Leader
Abraham Karkowsky, M.D., Ph.D., HFD-110, Medical Team Leader
John Lawrence, Ph.D., HFD-110, Statistician
Charles Resnick, Ph.D., HFD-110, Pharmacology Team Leader
Xavier Joseph, D.V.M., HFD-110, Pharmacologist
Kasturi Srinivasachar, Ph.D., Team Leader, Chemistry, Division of New Drug Chemistry I (HFD-810)
Nhi Nguyen, Pharm.D., HFD-860, Biopharmaceuticist
Khin Maung U, M.D., HFD-45, DSI, Medical Officer
Earl Butler, Ph.D., HFD-45, Pharmacologist
Edward Fromm, HFD-110, Consumer Safety Officer

Background

United Therapeutics has submitted this NDA for treprostinol sodium, a prostacyclin (PGI₂) analogue, for the treatment of pulmonary arterial hypertension. Studies for treprostinol sodium (formerly known as UT-15) were conducted under

Treprostinol sodium is related to Flolan (epoprostenol), a drug approved by the Agency on September 20, 1995 for primary pulmonary hypertension. Unlike Flolan which must be given through a central IV line, treprostinol is proposed to be given via a subcutaneous infusion pump.

The firm is requesting orphan product designation (and an exclusion from user fee payment) for the indication of pulmonary arterial hypertension.

An End-of-Phase 2 meeting was held on February 20, 1998 to discuss the design of phase 3 trials that would support filing of the NDA.

A Pre-NDA meeting was held on November 15, 1999.

Meeting

Pharmacology

Reviewer: Xavier Joseph, D.V.M.

Dr. Joseph had no objections to filing the NDA. He expects his review to be completed by February 28, 2001

Chemistry

Reviewer: Javher Advani, Ph.D.

Dr. Srinivasachar had no objections to filing the NDA. He said he expected Dr. Advani's review to be completed by January 31, 2001.

Facility inspections have been completed already.

Biopharmaceutics

Reviewer: Nhi Nguyen, Pharm.D.

Dr. Nguyen had no objections to filing the NDA. Dr. Nguyen expects her review to be completed by January 2, 2001.

Statistical

Reviewer: John Lawrence, Ph.D.

Dr. Lawrence had no objections to filing the NDA. The review is expected to be completed by January 2, 2001.

Medical

Medical Officers: Abraham Karkowsky, M.D., Ph.D.
Douglas Throckmorton, M.D.
Norman Stockbridge, M.D., Ph.D.

Dr. Karkowsky will review the two pivotal efficacy studies P01:04 and P01:05 while Dr. Throckmorton will review the remaining efficacy studies. Dr. Stockbridge will review safety. They expect their joint review to be completed by January 2, 2001.

Secondary Medical Review

Reviewer: Raymond Lipicky, M.D.

Dr. Lipicky expects to complete his review by January 15, 2001.

Division of Scientific Investigations

Dr. Lipicky and Karkowsky agreed that only 3 domestic sites would need inspection. Dr. U suggested inspections of the two pivotal studies sites based on high enrollments, relatively higher rates of dropouts and protocol deviations. Dr. Lipicky said this was acceptable.

Dr. Karkowsky asked that previous or concurrent anorexogenic drug use by patients in the studies be noted when doing the inspections. Dr. U said he would note this use when doing the inspections.

RHPM Filing Review

Application: NDA 21-272
Uniprost (treprostinol sodium) Injection
1.0, 2.5, 5.0, and 10 mg/ml

Applicant: United Therapeutics Corporation

Application Date: October 16, 2000

Receipt Date: October 16, 2000

User Fee Goal Date: April 16, 2001

Background

United Therapeutics has submitted this NDA for treprostinol sodium, a prostacyclin (PGI₂) analogue, for the treatment of pulmonary arterial hypertension. Studies for treprostinol sodium (formerly known as UT-15) were conducted under .

Treprostinol sodium is related to Flolan (epoprostenol), a drug approved by the Agency on September 20, 1995 for primary pulmonary hypertension. Unlike Flolan which must be given through a central IV line, treprostinol is proposed to be given via a subcutaneous infusion pump.

The firm is requesting orphan drug designation (and an exclusion from user fee payment) for this application. The company, on November 2, 1999, received an orphan product designation for "treatment of pulmonary arterial hypertension." The proposed indication in the draft labeling for Uniprost is the same but is being verified by the Office of Orphan Products Development before the issuance of an official exclusion from user fee payment.

Dr. Lipicky has granted a priority review of this drug and plans to take it before a Cardiovascular and Renal Advisory Committee Meeting in February 2001.

Meetings

End-of Phase 2: February 20, 1998
Pre-NDA: November 15, 1999

Reviewers:

Chemistry:	Javher Advani, Ph.D.
Microbiology:	Stephen Langille, Ph.D.
Biopharm:	Nhi Nguyen, Pharm.D.
Pharmacology:	Xavier Joseph, D.V.M.
Statistics:	John Lawrence, Ph.D.
Medical:	Douglas Throckmorton, M.D. Norman Stockbridge, M.D., Ph.D. Abraham Karkowsky, M.D., Ph.D.
Sec. Medical:	Raymond Lipicky, M.D.

Review

This NDA was submitted in paper with the CRF's being available electronically (through EDR).

The index to the NDA is adequate and the NDA overall appears to be well organized.

There are three controlled trials that support efficacy for this NDA with 2 studies (P01:04 and P01:05) that are considered pivotal.

The sponsor has requested a waiver for conducting pediatric studies pursuant to the Pediatric Rule.

The sponsor has submitted a Debarment Certification and Financial Interests and Arrangements of Clinical Investigators Certification.

Recommendation

Provided that the reviewers have not identified reasons for refusing to file, I recommend that the application be filed.

/S/

Edward Fromm
Regulatory Health Project Manager

cc: NDA 21-272
HFD-110
HFD-110/Fromm

dr: 10/30/00

Confirmation of Meeting

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

Sponsor: United Therapeutics Co.

Subject: Discussion of Post-Marketing Study

Date Meeting Requested: March 13, 2002
Date Confirmation Faxed: March 14, 2002

Meeting Date: March 28, 2002
Meeting Time: 11:30 A.M-1:00 P.M.

Location: Conference Room "F", 1451 Rockville Pike, Rockville, Md

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., HFD-110, Medical Team Leader
John Lawrence, Ph.D., HFD-110, Statistician
James Hung, Ph.D., HFD-110, Statistician/Team Leader
Natalia Morgenstern, HFD-110, Chief, Project Management Staff
Edward Fromm, HFD-110, Project Manager

Minutes of a Telecon between United Therapeutics and the FDA

Date: March 13, 2002

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

Applicant: United Therapeutics Co.

Subject: Labeling Issues and 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
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, 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. 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

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).

The focus of today's telecon were outstanding labeling issues; discussion about recent revisions the sponsor made to their post-marketing protocol would not begin until the Division has had adequate time to review them.

Telecon

Labeling

Dr. Temple said we agreed with the sponsor's revisions to the labeling with the following exceptions:

Post-Marketing Protocol

United Therapeutics said that revisions to the post-approval protocol were very recently sent to the Division. They said that they understand that the Division has not had an opportunity to review these revisions, but nevertheless would like to highlight some of the changes they have made:

- Revised protocol algorithm. The transition period from Flolan has been lengthened from 7 to 14 days. Patients not weaned off of Flolan at 14 days would be considered treatment failures. Dr. Throckmorton said it appears that there is no information on up-titrating the dose of Flolan if the patients are having difficulty being weaned off of Flolan. Dr. Karkowsky said the sponsor should also submit information about what number of up-titrations of Flolan would constitute a treatment failure.
- Added independent Adjudication Committee.
- Made minor clarifications to the primary and secondary end points of the study.

Minutes Preparation:


 Edward Fromm

Concurrence Chair:


 Robert Temple, M.D.

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

- Rd:
- JLawrence-3-19-02
 - JHung-3-20-02
 - NStockbridge-3-21-02
 - AKarkowsky-3-21-02
 - DThrockmorton-3-21-02
 - NMorgenstern-3-21-02

Minutes of a Telephone Conference Call between United Therapeutics and the FDA

Date: January 7, 2002

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

Sponsor: United Therapeutics

Subject: Discussion on the Outline of the Action Letter

FDA Participants:

Raymond Lipicky, M.D., Director, Division of Cardio-Renal Drug Products, HFD-110
Douglas Throckmorton, M.D., Deputy Division Director, HFD-110
Abraham Karkowsky, M.D., Medical Team Leader, HFD-110
Quynh Nguyen, Pharm.D., Regulatory Health Project Manager, HFD-110

United Therapeutics

Roger Jeffs, Ph.D., President
David Mottola, Ph.D., Vice President for Clinical and Scientific Affairs
Michael Wade, Ph.D., Associate Director, Research and Development
Carl Arneson, M.Stat., Associate Director, Biostatistics and Data Management
Dean Bunce, Sr. Director, Regulatory Affairs

Background

Remodulin (treprostinil sodium) Injection is a prostacyclin (PGI₂) analogue proposed for the treatment of pulmonary arterial hypertension. The New Drug Application (NDA) for Remodulin was originally submitted on October 16, 2000, but was withdrawn by United Therapeutics on July 5, 2001. Remodulin was presented before the Cardiovascular and Renal Drugs Advisory Committee on August 9, 2001. Subsequent to the Committee's 6-yes to 3-no vote that Remodulin be approved for pulmonary hypertension, United Therapeutics refiled the NDA on August 9, 2001. The resubmission was granted a priority review status with a goal date of February 9, 2002. This teleconference was scheduled to discuss the general outline of the action letter.

Meeting

Dr. Lipicky stated that the action letter to be issued by the February 9, 2002 goal date would not be an approval letter, but rather an approvable letter under Subpart H (21 CFR 314.500 - 314.560). The approvable letter will contain the conditions needed for approval under Subpart H and will include options for potential trial designs, labeling changes, and Phase 4 commitments.

Conclusion

The sponsor will be invited to meet with the Agency after issuance of the approvable letter to discuss the specifics of the conditions in the letter.

Minutes preparation: 1-9-02
Quynh Nguyen, Pharm.D.

Concurrence, Chair: Raymond Epicky, M.D. f

qn/1-8-02/1-9-02

rd: EFromm/1-8-02
AKarkowsky/1-9-02
DThrockmorton/1-9-02

cc: NDA 21-272
HFD-110
HFD-110/QNguyen
HFD-110/SMatthews

Minutes of a Telecon between United Therapeutics and the FDA

Date: June 8, 2001

Applications: NDA 21-272
Remodulin (treprostinol) Injection

Applicant: United Therapeutics

Subject: Division Feedback on Status of Review

FDA Participants:

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
Edward Fromm, HFD-110, Regulatory Health Project Manager

United Therapeutics

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

.ackground

Remodulin was submitted as NDA 21-272 on October 16, 2000 for the treatment of (PAH) pulmonary arterial hypertension. The drug was granted a priority review by the Division but has a user fee goal date of July 16, 2001 due to the submission of a major amendment to the NDA on April 12, 2001.

The Division requested a telecon with the sponsor to discuss the current status of the review as well as to ask the sponsor to consider presenting their application before the August Cardio-Renal Advisory Committee Meeting.

Telecon

Dr. Lipicky began the telecon by noting that the sponsor's recent submissions, although informative, did not appreciably change the Division's recommendation of a not approval action for the application. The sponsor asked why the Division's recommendation to Dr. Temple was still a not approvable one. Dr. Lipicky replied that the additional data submitted were retrospective analyses and the Division is still uncertain of the drug's clinical benefit. In addition, the need for pain medication while on the drug, especially opiates, is remarkable. The sponsor argued that although the drug causes infusion pain, the vast majority of the patients continue on therapy with the drug.

Dr. Lipicky said that the sponsor's arguments for the drug make the approvability decision a "close call" and therefore the presentation of the application before the August Cardio-Renal Advisory Committee Meeting might be helpful. Unfortunately, the Agency will have to make an approvable or not approvable decision on the application prior to the meeting. If the Advisory Committee rules in the sponsor's favor, the application could possibly be approved even if a not-approvable action has been taken. If an approvable letter is issued (with substantial changes to the labeling), the Advisory Committee can assist the Agency in labeling recommendations.

Ultimately though, the decision to go to the meeting is up to the sponsor.

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



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

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

This document is intended only for the use of the party to whom it is addressed and may contain information that is privileged, confidential, and protected from disclosure under applicable law. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to: CDER, DCRDP (HFD-110); 5600 Fishers Lane; Rockville, MD 20857

Transmitted to FAX Number: (919) 485-8352

Attention: Mr. Dean Bunce

Company Name: United Therapeutics Corporation

Phone: (919) 485-8350

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

Date: February 8, 2002

Pages including this sheet: 21

From: Edward Fromm

Phone: 301-594-5313

Fax: 301-594-5494

PLEASE LET ME KNOW THAT YOU RECEIVED THIS!!!!

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



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

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

This document is intended only for the use of the party to whom it is addressed and may contain information that is privileged, confidential, and protected from disclosure under applicable law. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to: CDER, DCRDP (HFD-110); 5600 Fishers Lane; Rockville, MD 20857

Transmitted to FAX Number: (919) 485-8352

Attention: Mr. Dean Bunce

Company Name: United Therapeutics

Phone: (919) 485-8350

Subject: Minutes of Telecon, March 12, 2001

Date: 03/26/01

Pages including this sheet: 4

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

Please notify us of any significant differences in understanding you may have regarding the meeting outcomes (as reflected in the minutes).

PLEASE LET ME KNOW YOU RECEIVED THIS. THANKS!

Minutes of a Telecon between United Therapeutics and the FDA

Date: March 12, 2001

Applications: NDA 21-272
Remodulin (treprostinol) Injection

Applicant: United Therapeutics

Subject: Division feedback on approvability recommendation

FDA Participants:

Raymond Lipicky, M.D., HFD-110, Director, Division of Cardio-Renal Drug Products
Douglas Throckmorton, M.D., HFD-110, Deputy Division Director
Abraham Karkowsky, M.D., Ph.D., HFD-110, Medical Team Leader
Edward Fromm, HFD-110, Regulatory Health Project Manager

United Therapeutics

James Crow, Ph.D., President and Chief Scientific Officer
Roger Jeffs, Ph.D., Director, Research, Development and Medical
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 (PAH) 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 telecon with the Division to discuss its recommendation that the application not be approved.

Telecon

United Therapeutics began the telecon by saying that they were not trying to change the Division's recommendation of non-approval but rather wanted guidance on what the major deficiencies of the application were and how they could correct them if the application was determined to be not-approvable by Dr. Temple. Dr. Lipicky replied that the major deficiencies were the following:

- There was a small treatment effect in the pivotal studies. Dr. Lipicky said that the mean treatment effect ranged from 3-6% of baseline; a small increase in exercise performance relative to baseline. He noted that sicker patients (NYHA Class IV) appeared to have greater increases in exercise performance than less sick (NYHA Class II) patients. Dr. Lipicky said this finding was interesting; the Division explored this potential benefit of the drug by plotting the point estimates of patients in the study versus exercise performance. It was found that a line with a positive slope could be drawn but that there was considerable scatter with the data points around that line. Thus, the hypothesis that sicker patients benefit much more than less ill patients will need to be confirmed with another study.
- Statistical significance was not achieved even when using the firm's fairly liberal statistical analysis plan; p values for both studies were greater than 0.05. Analyses by the Division were unable to add robustness to the results.

- Tolerance appears to develop to the drug over time.
- Dr. Lipicky said a concern of the Division, although not specifically a deficiency of the studies, is that the application did not appreciably study the effect of Remodulin on mortality and/or morbidity. Dr. Lipicky expressed concern that the availability of the sponsors' drug may interfere with patients receiving Flolan, an approved drug that has been shown to have an effect on mortality.

United Therapeutics said it appeared that certain population subsets of PAH obtained greater benefit from the drug than others did. They asked the Division if it would be possible to restrict the indication to a subset of population such as those patients with scleroderma. Dr. Lipicky said it was possible but that this hypothesis would have to be confirmed with another study.

Blinding of the study

The firm asked the Division if they believe that an unintentional bias was interjected into the study because of the way patients were classified when complaining of infusion site pain. Dr. Lipicky said that he accepts the results of the study at face value; he does not believe there was any bias, intentional or otherwise in the study.

Approvability of drug

The firm asked Dr. Lipicky what he thought were the chances of the drug being approved by Dr. Temple. Dr. Lipicky responded that it would be a "close call" but thought more likely than not, that the drug would not be approved. He said, however, that Dr. Temple might issue a not-approvable letter, but seek guidance on Remodulin at a future Cardio-Renal Advisory Committee meeting. If the Committee members were in favor of the drug, the not-approvable decision could be reversed.

The firm asked if the orphan designation of the drug would help in obtaining approval of the drug. Dr. Lipicky said he did not think it would influence Dr. Temple's decision making process.

Dr. Lipicky said it would be helpful for the firm to meet with Dr. Temple and the Division sometime in the week prior to the action date (April 16, 2001) for the application. He mentioned that the firm might want to bring clinical investigators from the trial, regulatory law and other experts to that meeting.

Open Label Study (P:1:06)

United Therapeutics asked what should they do with the approximately 600 patients who were currently using Remodulin in the open-label phase of the studies. Dr. Lipicky said the firm should first hear from Dr. Temple (about approvability of the drug) before making a final decision about these patients. If the drug is not approved, the firm should consider doing a randomized, withdrawal trial. The firm asked if they designed a double-blind, randomized, withdrawal trial in which patients received Remodulin or placebo and then had Remodulin as a rescue treatment, would that be acceptable to the Division. Dr. Lipicky replied that investigators might want to have Flolan as the rescue therapy. He said the endpoint could be time to rescue with Remodulin or Flolan. He added that the firm could also do a trial in the scleroderma subset of patients and have as the endpoint time to rescue with Flolan or Remodulin.

Dr. Lipicky said that another option would be to conduct a trial in NYHA class IV type patients and demonstrate that the drug improves walking distance from baseline significantly. The company

asked what level of statistical significance would be needed for such a study. Dr. Lipicky replied that the firm should aim for a p value as much less than 0.05 as possible.

The sponsor asked that if they conducted an IV infusion study and maximized the treatment effect of the drug, could they get an indication for both the IV and SQ routes of administration. Dr. Lipicky said they would not; any hypothesis(es) would need to be confirmed using the original SQ route of administration.

United Therapeutics asked that if they conducted another study (that the Agency agreed to), could the Agency issue an approvable letter that specified approval of the drug was conditional on successful results from the study. Dr. Lipicky said that he thought the Agency would not be receptive to that scenario. He said that if the Agency issues a not-approvable letter, it would be open to drafting a letter saying the successful completion of another study could lead to approval of the drug.

Conclusion

Dr. Lipicky said that the Division would be recommending non-approval of Remodulin to Dr. Temple but said that approval was still possible, although not likely. He suggested that the firm meet with Dr. Temple shortly before the due date of the application.

Dr. Lipicky and the firm discussed the outline of various studies, which in the event of an unfavorable approval decision by the Agency, could support eventual approval of the drug.

Minutes Preparation:

 /S/
Edward Fromm

Concurrence Chair:

 /S/
Raymond Lipicky, M.D. ✓

ef/3-14-01

Rd: DThrockmorton-3/16/01
AKarkowsky-3/16/01



Douglas C. Throckmorton, M.D.
Division of Cardio-Renal Drug Products, HFD-110

Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
Tel (301) 594-5327, FAX (301) 594-5494

Memorandum

DATE: 5.07.02

FROM: Douglas C. Throckmorton, M.D., Director
Division of Cardio-Renal Drug Products, HFD-110

TO: Robert Temple, M.D., Director
Office of Drug Evaluation-1, ODE-1

SUBJECT: Proposed post-approval study for Remodulin (UT-15), NDA 21-272

NAME OF DRUG: Remodulin (UT-15)

DOCUMENTS USED FOR MEMO:

1. Remodulin Complete Response dated 4.1.02.
2. Medical Officer Review or Complete Response by Avi Karkowsky, M.D., dated 4.18.02.

RECOMMENDATIONS

It is my recommendation that the trial as currently ^{proposal, RT} ~~trial~~, if completed, be deemed sufficient to meet our requirements stipulated in the Approvable letter dated 2.8.02. [^]

DISCUSSION

This memo is intended to provide the Divisional recommendation regarding the sufficiency of the proposed clinical study of Remodulin, P01:13, "A multicenter, randomized, parallel, placebo-controlled study of the efficacy and safety of subcutaneous remodulin therapy after transition from Flolan in patients with pulmonary arterial hypertension," submitted as a complete response to the approvable letter dated 2.8.02. This protocol has been the subject of multiple meetings, both internal and with the sponsor, as well as a through review by Dr. Karkowsky (where the reader is referred for additional details). Significant changes to the protocol since the last iteration include the addition of two more days of very low doses of Flolan before complete discontinuation (5% of starting dose for days 8, 9, and 10) and a clarification regarding the events that will be adjudicated (all discontinuations and all reinstatements of Flolan). Dr. Karkowsky has identified two areas of major concern of the current protocol that require comment:

- the difficulty in interpreting clinical changes that may occur while Flolan is being down-titrated and UT-15 is being instituted.
- the potential influence of the unblinding occurring as a result of infusion site pain in patients receiving UT-15.

Events Occurring During Down-Titration

The protocol-specified primary endpoint is the time to clinical deterioration defined as the time from initiation of study drug to earliest incidence of clinical worsening of PAH symptoms requiring reinstatement of Flolan therapy or re-hospitalization, or death. His concern, and mine, has to do with the interpretation of endpoints that occur at a time when Flolan is being down-titrated and UT-15 is being introduced. Since we don't know how slowly to withdraw Flolan to avoid rebound pulmonary hypertension, the effect of UT-15 to reduce events occurring during this time can be interpreted in two ways: UT-15 ameliorates rebound effects during Flolan withdrawal (which doesn't add much to our understanding of the efficacy of UT-15 in pulmonary hypertension), or UT-15 has a beneficial effect on pulmonary hypertension.

To address this concern the sponsor has extended the number of days at a very low level of Flolan prior to discontinuation from one to three days (an alternative deemed un-necessary was to continue a low dose of Flolan throughout the trial; I agree this would have been burdensome). They did not alter the endpoints to allow for one up titration of Flolan; their experts have asserted this would be unlikely to have a detectable acute effect and we cannot know otherwise. They have also clarified that all discontinuations from study drug and all reinstatutions of Flolan will be sent for adjudication.

Do I think this is an ideal trial to test the efficacy of UT-15? The alternative trial, a parallel group design comparing UT-15 to placebo on top of bosentan or Flolan, would have been more easily interpreted, although the current trial can certainly also assess the effectiveness of UT-15. The trial will be most interpretable if the largest fraction of patients complete their titration off Flolan and continue in the trial sufficient time to collect data on 6-minute walk, Borg Dyspnea and symptom scales. If substantial numbers of patients have symptoms consistent with rebound during withdrawal from Flolan, we will be left unable to confirm the clinical utility of the combined Borg Dyspnea/Walk surrogate (this is surely something we would like to understand better) and more importantly will be left to argue about the specifics of individual cases that decompensated during withdrawal from Flolan. We cannot know which scenario will occur without conducting the trial, and the sponsor has made every apparent reasonable effort to minimize the likelihood of rebound occurring during Flolan withdrawal. The current trial should be allowed to serve as the trial responding to the approvable letter.

Influence of Unblinded Assessment of Symptoms

Dr. Karkowsky continues to have serious reservations about the potential effects of unblinding on the assessment of clinical endpoints. While I share his concerns, the sponsor has made changes to the protocol to minimize the inclusion of pain information in data sent to the adjudication committee and mandated that all events be adjudicated by a committee blinded to treatment group. As above, they have also mandated that all discontinuations be sent to the committee (*i.e.*, those for site pain coexisting with worsening pulmonary symptoms). I see no additional steps that can reasonably be taken; while the issue of blinding remains relevant it is also true that symptomatic endpoints are clinically relevant when demonstrable. In this case, sufficient care has been taken to minimize the impact of the unblinding and the current trial should be allowed to serve as the trial responding to the approvable letter.

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**

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

/s/

Doug Throckmorton
5/7/02 07:12:46 AM
MEDICAL OFFICER



DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Memo

To: Dr. Robert Temple, Director, ODE-1

Re: NDA 21-272 (Remodulin)

Date: January 24, 2002

Reviewers: Raymond Lipicky, Division Director _____

Douglas C. Throckmorton, Deputy _____

Abraham Karkowsky, Team Leader _____

N. Stockbridge, Team Leader _____

/S/

/S/

/S/

/S/

1.24.02

1.25.02

This memo expands upon a memo dated 15 November 2001.

The primary medical reviews and the Division Director's memo concluded that remodulin should not be approved for pulmonary hypertension. At the meeting of 9 August 2001, the Cardio-Renal Advisory Committee, in a split vote, recommended approval. Subsequently, the four authors of this memo were polled to ask whether our judgements were affected by the Advisory Committee's deliberations or vote, and the replies were uniformly negative. This memo conveys a change of opinion and proposes how remodulin ought to be approved.

The chief issue for remodulin is whether the data are sufficiently compelling of clinical benefit. A case for benefit is difficult to make on the basis of the primary end points of the clinical studies—6-minute walking distance; the studies were adequately powered to detect the expected effect, but the observed effect was smaller than expected, so one is left with a marginal statistical result¹ and indeterminacy regarding whether the observed effects on exercise are reproducible or the products of chance.

In support of a treatment benefit, the sponsor called attention to a specified secondary end point, change in the Borg dyspnea score, a measure of shortness of breath at the end of the 6-minute walk. Recognizing the peril of trying to interpret a secondary end point in the presence of a nominally failed primary end point, the sponsor offered a retrospective analysis that combined the primary end point, 6-minute walking distance, and the Borg score, noting that both reflected the ability to exercise. The analysis ranked each subject's score on both tests, combined these rankings, and then re-ranked subjects based on the combined ranking. In this analysis, subjects on

¹ The studies were to be analyzed together, and they came close to, but did not meet, prespecified criteria for success. Differences in how a small number of dropouts are handled can make the p-value much larger and the evidence appear much weaker.

remodulin performed better than those on placebo on the combined exercise-Borg score end point. This outcome was highly statistically significant and is insensitive to the small number of withdrawals.

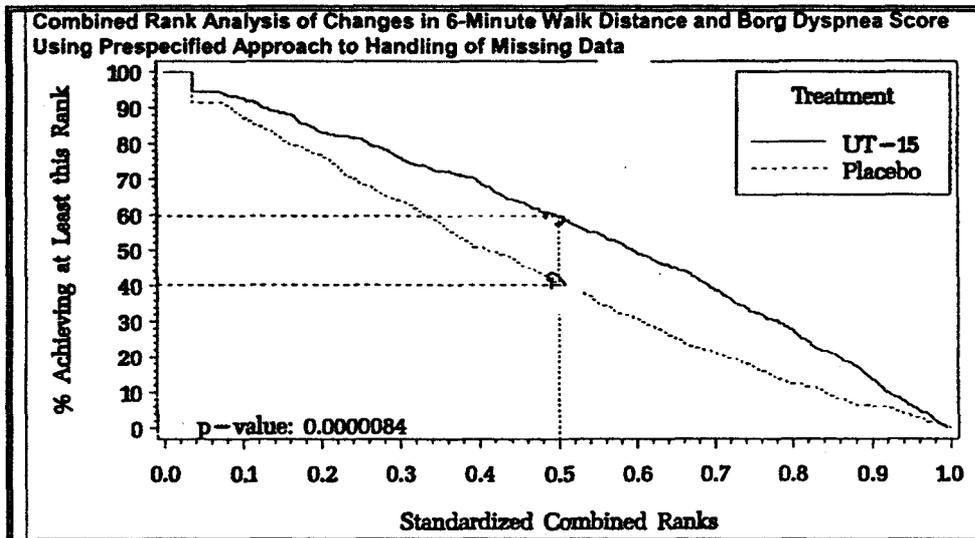


Figure 1. Sponsor's retrospective combined rank analysis of exercise and Borg score.

The Division reviewed the sponsor's retrospective ranked analysis of Borg score plus walking distance, and confirmed that the analysis achieved high nominal statistical significance. Furthermore, as noted in the medical review of 19 June 2001, the Borg component of the combined end point was less affected by informative censoring than other measurements of symptom benefit, since it was assessed by an investigator not otherwise involved in the subject's care.

The clinical interpretation of the combined, retrospective end point was and is unclear. What has changed is that the authors of this memo now believe that the combined end point is reasonably likely to predict a clinical benefit. Regulations permit such a drug to be approved, subject to a post-marketing trial to demonstrate a clinical benefit.

21CFR314.510 allows for approval "on the basis of ... an effect on a surrogate end point ... or on the basis of an effect on a clinical end point other than survival or irreversible morbidity." Remodulin's effects on Borg-plus-walking-distance clearly falls in the latter category. Remodulin falls within the scope of this provision as specified in 21CFR314.500, because pulmonary hypertension is a "serious or life-threatening illness" and remodulin has potential benefits (a better safety profile) compared with existing therapy (epoprostenol or bosentan).

If remodulin were to be approved under 21CFR314.510, United Therapeutics would be required to conduct an adequate and well-controlled study "verify[ing] ... clinical benefit". The regulation does not explicitly require the study to have an outcome end point.

Several trial designs could provide an acceptable demonstration of clinical benefit and fulfill the sponsor's obligations under 21CFR314.510.

The sponsor could choose to conduct a placebo-controlled withdrawal study, looking at either exercise or the first occurrence of death, hospitalization, or need for rescue therapy. Withdrawal could be performed in a stepwise manner to minimize any potential risk to the patients related to abrupt cessation of remodulin. This study could be conducted among patients now receiving open-label remodulin; any additional

subjects should enter a run-in, titration phase of at least 3 months. This study could also provide reassurance that remodulin remains effective during long-term use.

Alternatively and perhaps more feasibly, the sponsor could choose to evaluate the use of remodulin in a placebo-controlled study with a background of bosentan. The dosing regimen for remodulin could be the same as or different from that for remodulin as monotherapy. Acceptable end points might be mortal-morbid events, hospitalization, or exercise tolerance. This study would confirm the benefit of remodulin in subjects with pulmonary hypertension in combination with another medication.

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**



DIVISION OF CARDIO-RENAL DRUG PRODUCTS

Memo

To: Dr. Robert Temple, Director, ODE-I

Re: NDA 21-272 (Remodulin)

Date: November 15, 2001

Reviewers: Raymond Lipicky, Division Director

/S/

Douglas C. Throckmorton, Deputy

/S/

12/20/01

Abraham Karkowsky, Team Leader

/S/

12/03/01

N. Stockbridge, Team Leader

/S/

12/3/01

Primary medical reviews and the Division Director's memo concluded that remodulin should not be approved for pulmonary hypertension. At the meeting of 9 August 2001, the Cardio-Renal Advisory Committee, in a split vote, recommended approval. Subsequently, the four authors of this memo were polled to ask whether our judgements were affected by the Advisory Committee's deliberations or vote, and the replies were uniformly negative. This memo conveys a change of opinion and proposes how remodulin ought to be approved.

The chief issue for remodulin is whether the data are sufficiently compelling of clinical benefit. A case for benefit is difficult to make on the basis of the primary end points of the clinical studies; the studies were adequately powered to detect the expected effect, but the observed effect was smaller than expected, so one is left with a marginal statistical result and indeterminacy regarding whether the observed effects on exercise are reproducible or the products of chance.

In support of a treatment benefit, the sponsor called attention to a secondary end point, change in the Borg dyspnea score. The Division reviewed the sponsor's retrospective ranked analysis of Borg score plus walking distance, and concluded that the analysis achieved high nominal statistical significance, but the clinical interpretation was unclear.

21CFR314.510 allows for approval "on the basis of ... an effect on a surrogate endpoint ... or on the basis of an effect on a clinical end point other than survival or irreversible morbidity." Remodulin's effects on Borg-plus-walking-distance clearly falls in the latter category. Remodulin falls within the scope of this provision as specified in 21CFR314.500, because pulmonary hypertension is a "serious or life-threatening illness" and remodulin has potential benefits (a better safety profile) compared with existing therapy (epoprostenol or bosentan).

If remodulin were to be approved under 21CFR314.510, United Therapeutics would be required to conduct an adequate and well-controlled study "verify[ing] ... clinical benefit". The regulation does not explicitly require the study to have an outcome end point, although that is strongly implied. The details of such a trial will need to be worked out with the sponsor.

Please let the Division know if you are interested in additional discussions, or if you are interested in seeing a draft approval letter for UT-15 under 21CFR314.510.

**APPEARS THIS WAY
ON ORIGINAL**



Douglas C. Throckmorton, M.D.
Division of Cardio-Renal Drug Products, HFD-110

Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20816
Tel (301) 594-5327, FAX (301) 594-5494

Memorandum

DATE: 9.5.01
FROM: Douglas C. Throckmorton, M.D., Deputy Director
Division of Cardio-Renal Drug Products, HFD-110
TO: Robert Temple, M.D., Director
Office of Drug Evaluation I, ODE-I
SUBJECT: UT-15

Introduction

My opinion has not been changed by the Advisory Committee or the additional materials submitted by the sponsor in support of UT-15: the sponsor has not clearly demonstrated efficacy in the population studied at the doses of UT-15 studied. The reviewers and the sponsor all agree that the trials did not meet their pre-specified primary endpoint. The reviewers are also in general agreement that the primary analysis was 'close', whatever that means. The Advisory Committee took this closeness to allow for the examination of secondary endpoints, and (I believe) took sufficient support from those endpoints to vote for approval. As summarized below, I agree that the secondary endpoints are also 'close', but not convincing. In the end, I don't think the overall database provides a clear pattern of effectiveness on clinically-relevant endpoints. That informed individuals can disagree with that conclusion is manifest by the number of meetings, discussions, and memoranda around it.

The Data

Mortality/ Morbidity Endpoints

Leaving aside the primary endpoint, which has been analyzed and re-analyzed, what do we know about the other clinical endpoints? For all-cause mortality, there were few deaths, with not a hint of difference between the two treatment groups (see Table 1 below). Similarly, the rate of death or clinical worsening, and the rate of hospitalizations were both low in the controlled phase of the pivotal trials, although the numerical trends favored UT-15. The rate of deaths within 12 weeks or discontinuations due to transplant or clinical worsening requiring rescue therapy is summarized below.

Table 1. Selected Endpoints from Study P01:04/05

	Placebo	UT-15	Odds Ratio
Deaths ^a	10 (4.1%)	9 (3.9%)	--
Deaths/ Clinical Worsening ^a	16/236 (6.8%)	13/233 (5.6%)	0.81 (0.38-1.73)
Hospitalizations	40/236 (16.9%)	37/233 (15.8%)	--

a. Deaths during 12-week trial.

b. Deaths during the double-blind period (12 weeks), discontinuations due to transplant or clinical worsening requiring rescue therapy.

Hemodynamics

In the pivotal trials (P01:04/05) UT-15 had hemodynamic effects consistent with its pharmacology: increased cardiac output, decreased pulmonary and systemic vascular resistances, and decreases in mean pulmonary and right atrial pressures.

Effects on Symptoms of Pulmonary Hypertension

What do we know about the effect of UT-15 on symptoms of pulmonary hypertension? First, analysis of these endpoints is significantly complicated by the issue of site pain: roughly speaking, the subjects in the trials knew which treatment group they were receiving. As a result, the sponsor (and FDA) have focused attentions on those symptom scores thought to be relatively resistant to issues of unblinding: the Borg-dyspnea scale and various components of the symptom scores (especially syncope).

Borg-Dyspnea Scores

The changes in the Borg-dyspnea scores for UT-15 are summarized below, along with the data from bosentan. This comparison is useful in that bosentan had a robust efficacy compared with UT-15, and one might expect that the Borg-dyspnea scores would reflect that difference (that is, bosentan would look better). If the data are not consistent with this sense, it could call into question the UT-15 data, including as it relates to blinding issues. The improvements reported for UT-15 were similar to those reported for the highest dose of bosentan studied in the largest clinical trial of bosentan (352), and somewhat smaller than what was reported in study 351.

Table 2. Change in Borg-Dyspnea Score in UT-15 NDA.

UT-15	Placebo N=201	UT-15 N=212
P01:04		
Baseline Score ^a	4.3	4.4
Change from Baseline (12 Week)	+0.1	-0.9
Placebo-subtracted Effect	—	-1.0
P01:05		
Baseline Score ^a	4.4	4.2
Change from Baseline (12 Week)	+0.1	-0.9
Placebo-subtracted Effect	—	-1.0
P01:04/05 Combined		
Baseline Score ^a	4.4	4.4
Change from Baseline (12 Week)	+0.1	-0.9
Placebo-subtracted Effect	—	-1.0

a. Mean data shown. A reduction in the score represents improvement.

Table 3. Change in Borg-Dyspnea Score in Bosentan NDA.

Bosentan	Placebo	Bosentan 125 mg ^b	Bosentan 250 mg
Study 352	N=69	N=74	N=70
Baseline Score ^a	3.8	3.3	3.8
Change from Baseline (16 Week)	+0.3	-0.1	-0.6
Placebo-subtracted Effect	—	-0.4	-0.9
Study 351	N=11	N=21	
Baseline Score ^a	4.2	4.4	—
Change from Baseline (12 Week)	+1.4	-0.2	—
Placebo-subtracted Effect	—	-1.6	—

a. Borg-Dyspnea score measured from 0 (no perceived exertion) to 10 (maximal) at the end of the 6-minute walk.

b. Bosentan dosing BID.

Symptom Measures

The sponsor also analyzed individual symptoms of congestive heart failure in the two UT-15 pivotal trials. These analyses are reproduced below to make two points: first, a trend towards more resolution and decreased development was seen for all of the symptoms; second, most of the symptoms were relatively non-specific (e.g., dyspnea, dizziness, edema) and open to bias if the patient knew which treatment they were receiving.

Table 4. Individual Symptoms of CHF with UT-15^a.

Symptom	Resolved Completely		Newly-Developed	
	UT-15	Placebo	UT-15	Placebo
Dyspnea	1	2	0	2
Fatigue	0	2	12	17
Dizziness	18	10	38	50
Chest Pain	25	17	24	50
Syncope	13	8	3	9
Orthopnea	8	6	31	47
Palpitations	20	8	46	34
Edema	13	12	34	41

a. Data for symptoms occurring any time during 12-week double blind period compared with 4 weeks prior to randomization, as collected by CRF check-box.

It was suggested by the sponsor and their consultants that some of these symptoms are less susceptible to unblinding issues than others; that some symptoms were 'severe' or 'unexpected' enough that knowledge of treatment would not significantly alter their reporting. Of the list above, syncope was the focus of much discussion, and the numbers initially sent to the Division suggested that UT-15 indeed had an effect to reduce the development of syncope (row 1 in the table below). Below are data summaries prepared since the Advisory Committee, looking in addition at the reported of syncope at different times during the patient's disease. The last row is most inclusive; collecting historical data from any time prior to enrollment in the trial. When all patients who had had syncope at any time in the past were queried, the differences between the two treatment groups were less substantive.

Table 5. Reporting of Syncope in UT-15^a.

Syncope	Resolved Completely		Newly-Developed	
	UT-15	Placebo	UT-15	Placebo
Last 6 weeks of dbl-blind vs. 4 weeks prior to randomization	15	11	1	7
Any time during double-blind therapy vs. 4 weeks prior to randomization	13	8	3	9
Any time during double-blind therapy vs. any time in the past	57	49	2	4

a. Data for symptoms occurring any time during 12-week double blind period compared with 4 weeks prior to randomization, as collected by CRF check-box.

b. From sponsor's submission dated 8.16.01.

Safety

Just a brief comment on the use of narcotic analgesics for site pain. The sponsor has submitted materials that convince me of three things. First, a significant percentage of patients were still taking narcotics in the long-term open-label trials when contacted (8% in last day, more during the week before the interview). Second, not all centers required narcotics, suggesting that other factors relevant to individual centers could be accounting for some of the narcotic use. Finally, there was no clear evidence of harm that was linked to the use of narcotics, although the more subtle impairments (driving etc.) would not have been captured. Given that, I am now convinced that site pain is a management issue in this population and not an impediment to approval.

Conclusions

Why go through all these analyses? While some of them have not been shown to you previously, their primary importance is that they fit a pattern I believe describes the NDA database for UT-15: 'close.' For the endpoints we care about, from the pre-specified primary through the most post-hoc dredged-out secondary endpoint, the data lean without being definitive. When the primary endpoints is examined, any robustness analysis weakens the statistical strength of the treatment difference. When the secondary endpoints (such as Borg-dyspnea or syncope) are examined, their interpretation similarly becomes less clear-cut. At some point, of course, the number of 'leans' can overcome difficulties with an individual endpoint or analysis. I don't know where that is, but cannot conclude UT-15 is in that place. That being said, I can't recommend approval. While sympathetic to the needs of the population, additional data are needed in this case to clearly define the effectiveness of UT-15 in this population.

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

/s/

Doug Throckmorton
9/5/01 11:18:53 AM
MEDICAL OFFICER

MEMORANDUM

DATE: January 10, 2002

FROM: Xavier Joseph, D.V.M., Pharmacologist, HFD-110

THROUGH: Charles Resnick, Ph.D, Supervisory Pharmacologist, HFD-110

TO: Edward Fromm, Regulatory Health Project Manager, HFD-110

SUBJECT: NDA 21-272

REMODULIN™ Injection (treprostinol sodium)
Draft Product Labeling Revisions

As per Dr. David Morse's suggestions, the draft product label should be revised as follows:

A) Under the heading of "Carcinogenesis, Mutagenesis and Impairment of Fertility", the following sentences (*italicized*) should be added at the end of the text. "*In this study, males were dosed for 10 weeks prior to mating and _____ through the 2 week mating period. Females were dosed for 2 weeks prior to mating _____ till gestational day 6.*"

B) Under the heading of "Pregnancy", the text should be replaced with the following.

◆ *Pregnancy Category B. In pregnant rats, continuous subcutaneous — infusion of treprostinol sodium during the period of organogenesis and late gestational development, at rates as high as 900 ng treprostinol/kg/min (about 117 times the starting human rate of infusion, on a ng/m² basis and about 16 times the average rate achieved in clinical trials), resulted in no evidence of harm to the fetus. In pregnant rabbits, — effects of continuous subcutaneous infusion of treprostinol during organogenesis were limited to an increased incidence of fetal skeletal variations (bilateral full rib or right rudimentary rib on lumbar 1) associated with maternal toxicity (reduction in body weight and food consumption) at an infusion rate of 150 ng treprostinol/kg/min (about 41 times the starting human rate of infusion, on a ng/m² basis, and 5 times the average rate used in clinical trials). In rats, continuous — infusion of treprostinol sodium from implantation to the end of lactation, at rates of up to 450 ng treprostinol/kg/min, did not affect the growth and development of the offspring. Because animal reproduction studies are not always predictive of human response, Remodulin should be used during pregnancy only if clearly needed.*

C) A new section on "Labor and Delivery" should be added after the section on "Pregnancy".

◆ *Labor and Delivery: No treprostinol sodium treatment-related effects on labor and delivery were seen in animal studies. The effect of treprostinol sodium on labor and delivery in humans is unknown.*

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

/s/

Xavier Joseph
1/15/02 11:47:05 AM
PHARMACOLOGIST
Draft Labeling Revisions

Charles Resnick
1/18/02 09:20:35 AM
PHARMACOLOGIST

Memorandum

Date: 30 Oct. 2001

From: David E. Morse, Ph.D. /S/
Asc. Director (Pharm./Tox.), ODEI

To: Robert Temple, M.D.
Director, Office of Drug Evaluation I

Cc: Raymond Lipicky, M.D., Dir., DCRDP (HFD-110)
-Charles Resnick, Ph.D., TL Pharm./Tox., DCRDP (HFD-110)

Subject: NDA 21-272
REMODULIN™ Tablets (treprostinol sodium)
Review of Pharm./Tox. Labeling

I. Materials Included in Review

1. Pharm./Tox. Review of NDA 21-272, dated 12 March 2001, written by X. Joseph, DVM
2. NDA 21-272 Action Package (26 Oct. 2001) with Draft Product Labeling (14 March 2001; 15:19.00)

II. Related Product Information

1. Product label for FLOLAN™ for Injection

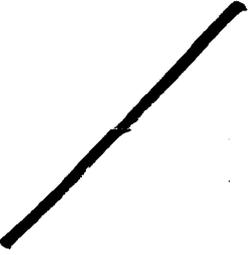
III. Background

The sponsor (United Therapeutics Corp.) is seeking approval of REMODULIN™ Injection (treprostinol sodium) for use in the long-term treatment of pulmonary arterial hypertension (NYHA Class II-IV). Treprostinol, a tricyclic benzidine analogue of epoprostinol (prostacyclin PGI₂), has both venous and arterial vasodilatory effects, which reduces cardiac afterload and increases cardiac output and stroke volume. Treprostinol also demonstrates inhibitory effects on platelet aggregation in vitro and in vivo. Since pulmonary arterial hypertension is frequently a chronic disease, patients would be expected to potentially undergo extended duration of dosing with REMODULIN™.

IV. Comments related to the Draft Product Label

A) Under the heading of "Carcinogenesis, Mutagenesis and Impairment of Fertility" it is recommended that:

B) Under the heading of "Pregnancy" it is recommended that:

- 
- C) although REMODULIN™ is not indicated for use in pregnant women, the draft product label should be revised to include a section on "Labor and Delivery" and describe those effects noted in the relevant animal toxicology studies,

V. Summary

A review of the action package for NDA 21-272, REMODULIN™ Injection, suggests that the product has been adequately evaluated in multiple non-clinical safety studies (continuous sc infusion studies up to 26 weeks duration in the rat and dog, genotoxicity and reproductive toxicity studies) for potential approval. The proposed product label, with minor revision as suggested in the preceding section of this memorandum, adequately reflects the non-clinical safety data for this product.

APPEARS THIS WAY
ON ORIGINAL

MEMO

To: Raymond Lipicky, MD
Director, Division of Cardio-Renal Drug Products, HFD-110

From: Kevin Dermanoski
Safety Evaluator, Division of Medication Errors and Technical Support, HFD-400

Through: Carol Holquist, RPh
Deputy Director, Division of Medication Errors and Technical Support, HFD-400

CC: Edward J. Fromm
Project Manager, Division of Cardio-Renal Drug Products, HFD-110

Date: January 18, 2002

Re: ODS Consult 00-0283-2; Remodulin (Treprostinol Sodium Injection); NDA 21-272

This memorandum is in response to a January 10, 2002, request from your Division for a re-review of the proprietary name, Remodulin. The expected approval date for this application is March 2002.

The Division of Medication Errors and Technical Support (DMETS) has not identified any additional proprietary or established names that have the potential for confusion with Remodulin since we conducted our initial review on January 9, 2001 (OPDRA consult 00-0283), and our follow-up review on September 21, 2001 (OPRDA consult 00-283-01), that would render the name objectionable. Therefore, we have no objections to the use of this proprietary name.

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 before NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward.

If you have any questions or need clarification, please contact the medication errors project manager, Sammie Beam at 301-827-3231.

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

/s/

Kevin Dermanoski
1/18/02 10:28:50 AM
CSO

Carol Holquist
1/18/02 10:43:24 AM
PHARMACIST

Memo

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

From: Jerry Phillips, R.Ph.
Associate Director, Office of Post-Marketing Drug Risk Assessment
HFD-400

CC: Edward Fromm
Project Manager, HFD-110

Date: September 21, 2001

Re: OPDRA Consult 00-0283-1; Remodulin (Treprostinol Sodium Injection); NDA 21-272

This memorandum is in response to a September 7, 2001, request from your Division for a re-review of the proprietary name, Remodulin. The expected approval date for this application is October 15, 2001.

OPDRA has not identified any additional proprietary or established names that have the potential for confusion with Remodulin since we conducted our initial review on January 9, 2001 (OPDRA consult 00-0283), that would render the name objectionable. Therefore, we have no objections to the use of this proprietary name.

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 before NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward.

If you have any questions or need clarification, please contact the medication errors project manager, Sammie Beam at 301-827-3231.

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

/s/

Carol Holquist
9/26/01 10:27:50 AM
PHARMACIST

Jerry Phillips
9/26/01 11:47:26 AM
DIRECTOR

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



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

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

This document is intended only for the use of the party to whom it is addressed and may contain information that is privileged, confidential, and protected from disclosure under applicable law. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to: CDER, DCRDP (HFD-110); 5600 Fishers Lane; Rockville, MD 20857

Transmitted to FAX Number: (919) 485-8352

Attention: Mr. Dean Bunce

Company Name: United Therapeutics

Phone: (919) 485-8350

Subject: Minutes of meeting w/FDA on March 28, 2002
Remodulin (treprostinil sodium) Injection
NDA 21-272

Date: April 11, 2002

Pages including this sheet: 4

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

PLEASE LET ME KNOW YOU RECEIVED THIS. THANKS!

MESSAGE CONFIRMATION

04/11/02 15:33
ID=FDA CDER DCRDP

NO.	MODE	BOX	GROUP
477	TX		

DATE/TIME	TIME	DISTANT STATION ID	PAGES	RESULT	ERROR PAGES	S. CODE
04/11 15:31	01'13"	919 485 8352	004/004	OK		0000

DIVISION OF CARDIO-RENAL DRUG PRODUCTS FOOD AND DRUG ADMINISTRATION



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

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

This document is intended only for the use of the party to whom it is addressed and may contain information that is privileged, confidential, and protected from disclosure under applicable law. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to: CDER, DCRDP (HFD-110); 5600 Fishers Lane; Rockville, MD 20857

Transmitted to FAX Number: (919) 485-8352

Attention: Mr. Dean Bunce

Company Name: United Therapeutics

Phone: (919) 485-8350

Subject: Minutes of meeting w/FDA on March 28, 2002
Remodulin (treprostinil sodium) Injection
NDA 21-272

Date: April 11, 2002

Pages including this sheet: 4

MESSAGE CONFIRMATION

03/21/02 15:13
ID=FDA CDER DCRDP

NO.	MODE	BOX	GROUP
266	TX		

DATE/TIME	TIME	DISTANT STATION ID	PAGES	RESULT	ERROR PAGES	S. CODE
03/21 15:12	01'38"	919194858352	005/005	OK		0000

DIVISION OF CARDIO-RENAL DRUG PRODUCTS FOOD AND DRUG ADMINISTRATION



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

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

This document is intended only for the use of the party to whom it is addressed and may contain information that is privileged, confidential, and protected from disclosure under applicable law. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to: CDER, DCRDP (HFD-110); 5600 Fishers Lane; Rockville, MD 20857

Transmitted to FAX Number: (919) 485-8352
Attention: Ms. Lavonne Stagg-Hope
Company Name: United Therapeutics
Phone: (919) 485-8350
Subject: Minutes of meeting w/FDA on March 7, 2002
Remodulin (treprostinil sodium) Injection
NDA 21-272
Date: March 21, 2002

Pages including this sheet: 4

MESSAGE CONFIRMATION

03/14/02 15:52
ID=FDA CDER DCRDP

NO.	MODE	BOX	GROUP
191	TX		

DATE/TIME	TIME	DISTANT STATION ID	PAGES	RESULT	ERROR PAGES	S. CODE
03/14 15:51	00'30"	919194858352	002/002	OK		0000

DIVISION OF CARDIO-RENAL DRUG PRODUCTS FOOD AND DRUG ADMINISTRATION



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

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

This document is intended only for the use of the party to whom it is addressed and may contain information that is privileged, confidential, and protected from disclosure under applicable law. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to: CDER, DCRDP (HFD-110); 5600 Fishers Lane; Rockville, MD 20857

Transmitted to FAX Number: (919) 485-8352

Attention: Mr. Dean Bunce

Company Name: United Therapeutics

Phone: (919) 485-8350

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

Date: March 14, 2002

Pages including this sheet: 2

MESSAGE CONFIRMATION

03/07/02 10:34

ID=FDA CDER DCRDP

NO.	MODE	BOX	GROUP
103	TX		

DATE/TIME	TIME	DISTANT STATION ID	PAGES	RESULT	ERROR PAGES	S. CODE
03/07 10:31	03'13"	919194858352	013/013	OK		0000

DIVISION OF CARDIO-RENAL DRUG PRODUCTS FOOD AND DRUG ADMINISTRATION



US Mail address:
FDA/CDER/HFD-110
5800 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

This document is intended only for the use of the party to whom it is addressed and may contain information that is privileged, confidential, and protected from disclosure under applicable law. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to: CDER, DCRDP (HFD-110); 5800 Fishers Lane; Rockville, MD 20857

Transmitted to FAX Number: (919) 485-8352

Attention: Mr. Dean Bunce

Company Name: United Therapeutics

Phone: (919) 485-8350

Subject: Minutes of meeting w/FDA on February 13, 2002
Remodulin (treprostinil sodium) Injection
NDA 21-272

Date: March 7, 2002

Pages including this sheet: 13