CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-272

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

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Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**21-272**	**Brand Name**	**Remodulin™**
OCPB Division (I, II, III)	**I**	**Generic Name**	**Treprostinol sodium, UT-15**
Medical Division	**Cardio-Renal Drug Products**	**Drug Class**	**Prostacyclin analogue**
OCPB Reviewer	**B. Nhi Nguyen & Jogarao Gobburu**	**Indication(s)**	**Pulmonary artery hypertension**
OCPB Team Leader	**Angelica Dorantes**	**Dosage Form**	**Injection**
		Dosing Regimen	**1.25 ng/kg/min x 1 wk, then increase weekly by a maximum of 1.25 ng/kg/min. After 4 wks, increase weekly by a maximum of 2.5 ng/kg/min**
Date of Submission	**10/16/00**	**Route of Administration**	**Continuous subcutaneous infusion**
Estimated Due Date of OCPB Review	**3/16/01**	**Sponsor**	**United Therapeutics Corp.**
PDUFA Due Date	**4/16/01**	**Priority Classification**	**1PV**
Division Due Date	**3/16/01**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:	X	1	1	
Isozyme characterization:				
Blood/plasma ratio:	X	1	1	
Plasma protein binding:	X	1	1	
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
acute dose:	X	1	1	
chronic dose:	x	1	1	
Patients-				
acute dose:				
chronic dose:				
Dose proportionality -				
fasting / non-fasting acute dose:	X	1	1	
fasting / non-fasting chronic dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	1	1	
In-vivo effects of primary drug:	X	1	1	
In-vitro:	X	1	1	
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:	X	1	1	

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PD:	[redacted]	[redacted]	[redacted]	[redacted]
Phase 2:				
Phase 3:				
PK/PD:	[redacted]	[redacted]	[redacted]	[redacted]
Phase 1 and/or 2, proof of concept:	X	1	1	
Phase 3 clinical trial:	x	1	1	
Population Analyses -	[redacted]	[redacted]	[redacted]	[redacted]
Data rich:				
Data sparse:				
II. Biopharmaceutics	[redacted]	[redacted]	[redacted]	[redacted]
Absolute bioavailability:	X	2	2	
Relative bioavailability -	[redacted]	[redacted]	[redacted]	[redacted]
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -	[redacted]	[redacted]	[redacted]	[redacted]
traditional design; acute / multi dose:				
replicate design; acute / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies	[redacted]	[redacted]	[redacted]	[redacted]
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	[redacted]	11	11	

Filability and QBR comments

	"X" if yes	*Comments*
Application filable ?	x	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?	N/A	Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	1a. Is there an exposure-response relationship? b. If yes, does tolerance develop to UT-15? 2. Has the metabolism of UT-15 been adequately characterized?	
Other comments or information not included above		
Primary reviewer Signature and Date PM reviewer Signature and Date	B. Nhi Nguyen 3/05/01 Jogarao Gobburu 3/05/01	
Secondary reviewer Signature and Date	Angelica Dorantes 3/05/01	

CC: NDA 21-272, HFD-850(Electronic Entry or Lee), HFD-110(CSO), HFD-860(Dorantesa, Mehta), CDR (B. Murphy)

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA:	21-272	**SUBMISSION DATES**
TYPE:	1PV	Original NDA 10/16/00
BRAND NAME:	Remodulin™	Original amendment N-BB 1/25/01
GENERIC NAME:	treprostinol sodium	Original amendment N-BB 2/28/01
ALTERNATE NAMES:	UT-15, uniprost, LRX-15, 15AU81, BW A15AU, U-62,840	
DOSAGE STRENGTH:	1.0, 2.5, 5.0, 10.0 mg/mL injection	
SPONSOR:	United Therapeutics Corp.	

DIVISION OF PHARMACEUTICAL EVALUATION: I
PRIMARY REVIEWER: B. Nhi Nguyen, Pharm.D.
PHARMACOMETRICS REVIEWER: Jogarao Gobburu, Ph.D.
TEAM LEADER: Angelica Dorantes, Ph.D.

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RECOMMENDATIONS

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed NDA 21-272 and find the clinical pharmacology and biopharmaceutics section acceptable provided the following **comments to the sponsor** are addressed:

1. The sponsor should identify the enzymes responsible for the metabolism of UT-15.
2. The sponsor should make every effort to identify the fifth metabolite (HU1).
3. The sponsor should make every effort to determine the activity of all five metabolites.
4. Labeling comments #1 - 7 should be adequately addressed if the medical officer also concurs.

COMMENTS TO THE MEDICAL OFFICER

1. Exposure-Response

The PK/PD analysis performed on the P01:04/05 data shows that UT-15 has a statistically significant effect on the hemodynamic variables PAPm, CI, SvO_2 and PVRI, and dyspnea (BORG score). Additionally, the change in PAPm correlated with the distance walked in six minutes by the patients. Although these relationships were statistically significant, the slope of the relationship was very shallow. Based on the shallow slope and the EC_{50} derived from *in-vitro* experiments, the data are probably in the lower part of the exposure – response curve. Although uncertain, crude analysis suggests a dose-dependent opiate (surrogate for injection site pain) use.

2. Tolerance

We were unable to assess if patients develop tolerance to UT-15 with respect to its effect on PAPm. Although uncertain, crude analysis suggests a dose-dependent opiate (surrogate for injection site pain) use. Both PAPm and injection site pain are biomarkers of pulmonary and systemic vasodilation. Tolerance implies that higher exposure of the drug not necessarily produces proportionally greater effects. The fact that the PAPm was measured once at baseline and once towards the end of the study will not permit explorations of whether tolerance develops to UT-15. The frequency of patients with pain is dependent on dose rate in the P01:04/05 studies. The percentage of patients receiving opiates did not decrease at higher dose rates.

3. Dose adjustment for body size

Analysis of studies P01:04/05 and P01:09 data suggest that dosing adjusted for ideal body weight (IBW) is more appropriate than dosing based on total body weight. The volume of distribution at steady state is not very large (~50 L/kg in a 70 kg IBW person) implying that the drug is not distributed into deeper adipose tissues.

4. Hepatic insufficiency (HI)

The sponsor studied patients with mild and moderate HI. The sponsor found that patients with mild and moderate HI have 2x and 4x higher Cmax, respectively, and 3x and 5x higher $AUC_{0\text{-inf}}$

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