DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Martine Rothblatt, Ph.D., J.D., M.B.A.
Chairman and Chief Executive Officer
United Therapeutics Corporation
1110 Spring Street
Silver Spring, MD 20910

Re: NDA #21-272
Remodulin® (treprostinil sodium) Injection
MACMIS #12847

WARNING LETTER

Dear Dr. Rothblatt**:**

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a professional journal advertisement (ad) for Remodulin® (treprostinil sodium) Injection which appeared in the Winter 2003 and Spring 2004 issues of *Scleroderma Care and Research*, and a Medical Frequently Asked Questions booklet (booklet) for the product submitted by United Therapeutics Corporation under cover of Form FDA 2253 in response to an inquiry letter from DDMAC dated June 21, 2004. DDMAC has concluded that the ad and booklet are false or misleading because they minimize risk information, make unsubstantiated effectiveness claims and omit material facts. In addition, the booklet makes unsubstantiated comparative claims. The ad and booklet thus misbrand the drug in violation of the Federal Food, Drug, and Cosmetic Act (Act) (21 U.S.C. 352(a), (n); 321(n)), and FDA's implementing regulations, 21 CFR 202.1(e)(5)(i), (iii); (e)(6)(i). In addition, it appears that the FDA-approved product labeling (PI) for Remodulin did not accompany the Medical Frequently Asked Questions booklet, in violation of 21 CFR 201.100(d), and that these materials were neither submitted to FDA on Form FDA 2253 at the time of initial dissemination or initial publication, as required by 21 CFR 314.81(b)(3)(i), nor submitted to FDA 30 days prior to the intended time of initial dissemination or initial publication as required by 21 CFR 314.550. These promotional materials raise significant public health and safety concerns because they suggest that Remodulin is safer and more effective than has been demonstrated by substantial evidence or substantial clinical experience, and that Remodulin is superior to a treatment with proven efficacy and survival benefits.

Background

Remodulin was approved as an accelerated approval drug in accordance with 21 CFR 314.510. According to the Indications and Usage section of the PI, Remodulin "is indicated as a continuous subcutaneous infusion for the treatment of pulmonary arterial hypertension in patients with NYHA Class II-IV symptoms to diminish symptoms associated with exercise."

The Adverse Reactions section of the PI states:

> Patients receiving Remodulin reported a wide range of adverse events, many potentially related to the underlying disease (dyspnea, fatigue, chest pain, right ventricular heart failure, and pallor). During clinical trials infusion site pain and reaction were the most common adverse events among those treated with Remodulin. Infusion site reaction was defined as any local adverse event other than pain or bleeding/bruising at the infusion site and included symptoms such as erythema, induration or rash. Infusion site reactions were sometimes severe and could lead to discontinuation of treatment.
>
> Other adverse events included diarrhea, jaw pain, edema, vasodilatation and nausea.

In addition, as described in the Adverse Reactions section of the PI, severe infusion site reaction and pain were experienced by 38% and 39% of Remodulin treated patients, respectively, and 32% of patients required a prescription for narcotics.

The Adverse Reactions section of the PI describes adverse events attributable to the drug delivery system in pulmonary arterial hypertension controlled trials, as follows:

> There were no reports of infection related to the drug delivery system. There were 187 infusion system complications reported in 28% of patients (23% Remodulin, 33% placebo); 173 (93%) were pump related and 14 (7%) related to the infusion set. Most delivery system complications were easily managed (e.g., replace syringe or battery, reprogram pump, straighten crimped infusion line). Eight of these patients (4 Remodulin, 4 Placebo) reported non-serious adverse events resulting from infusion system complications. Adverse events resulting from problems with the delivery systems were typically related to either symptoms of excess Remodulin (e.g., nausea) or return of PAH symptoms (e.g., dyspnea). These events were generally resolved by correcting the delivery system pump or infusion set problem. Adverse events resulting from problems with the delivery system did not lead to clinical instability or rapid deterioration.

The Clinical Effects section of the PI states:

> The effect of Remodulin on 6-minute walk, the primary end point of the studies, was small and did not achieve conventional levels of statistical significance. For the combined populations, the median change from baseline on Remodulin was 10 meters and the median change from baseline on placebo was 0 meters. Although it was not the primary endpoint of the study, the Borg dyspnea score was significantly improved by Remodulin during the 6-minute walk, and Remodulin also had a significant effect, compared with placebo, on an assessment that combined walking distance with the Borg dyspnea score.

The promotional materials that are the subject of this letter contain, among other things, claims comparing Remodulin to Flolan, another drug indicated for the long-term intravenous treatment of primary pulmonary hypertension and pulmonary hypertension associated with the scleroderma spectrum of disease in NYHA Class III and Class IV patients who do not respond adequately to conventional therapy. In contrast to Remodulin's PI, the PI for Flolan (epoprostenol sodium) indicates that Flolan demonstrated statistically significant improvement in exercise capacity, as

measured by the 6-minute walk test. In addition, Flolan improved survival in NYHA functional Class III and Class IV primary pulmonary hypertension patients.

Unsubstantiated Effectiveness Claims

The ad includes a graph entitled, "Effect of Treprostinil on Distance and Symptoms During 6-Minute Walk Test" and the claim, "Significant improvement in exercise tolerance (walk distance) occurred when effective doses were reached." The graph indicates that the effect of Remodulin on walk distance was greater than 10 meters. DDMAC is not aware of substantial evidence or substantial clinical experience to support this claim in the ad. Indeed, the PI indicates that the change in walk distance was only 10 meters and that the effect on walk distance was not statistically significant. The graph and claim are thus misleading because they imply that Remodulin had a statistically significant effect on walk distance and that the effect on walk distance exceeded 10 meters when neither proposition has been demonstrated by substantial evidence or substantial clinical experience.

The ad also includes a graph entitled, "Change in Exercise vs. Treprostinil Dose at Week 12." This graph implies that a dose-response effect on walk distance has been demonstrated. This graph cites studies that do not constitute substantial evidence or substantial clinical experience supporting such a presentation. Specifically, it is inappropriate to retrospectively analyze data from failed studies in an attempt to relate walking distance to dose achieved because patients on any given dose do not represent patients randomly assigned to that dose. They may, therefore, differ in unrecognized ways that are themselves related to walking distance. A comparison of walk distance to dose achieved where the populations receiving various doses is not randomly chosen is not interpretable, and does not constitute evidence of dose-response or evidence of effectiveness.

Misleading Comparative Claims/Omission of Material Facts

The booklet asks the question, "**How is Remodulin Therapy different from Flolan Therapy?**" It then highlights the putative advantage of Remodulin: that it is given subcutaneously, as opposed to the central infusion needed for Flolan. However, because of the open ended nature of the question, a complete comparison is called for, but is not provided. For example the answer fails to disclose the material facts that Flolan has a proven effect on walking distance and survival in the indicated patient population while Remodulin has <u>not</u> demonstrated these benefits. The 6-minute walk that was improved by Flolan but not Remodulin was the primary endpoint in the studies of both drugs, and improved survival in advanced stage pulmonary hypertension is of obvious importance.

Additionally, the booklet contains a presentation under the heading "Can I Switch From Flolan to Remodulin?" that suggests that such a switch would be a successful therapeutic option (claiming "Yes in fact there were published results of a study where patients were successfully switched from Flolan to Remodulin") and that suggests that Remodulin offers advantages over Flolan, noting that "[p]atients on Remodulin compared to Flolan have more freedom of movement and activities due to a smaller pump and no surgically placed catheter to administer the drug." As with the previous presentation, the answer fails to disclose the material facts that Flolan has a proven effect on walking distance and survival in the indicated patient population while Remodulin has not demonstrated these benefits. Furthermore, the conclusion offered in the presentation that patients can successfully switch from Flolan to Remodulin is misleading because there is no substantial evidence or substantial clinical experience that supports that such a switch would be a successful treatment option for

patients. The study cited to support the claims, an uncontrolled, open-label study in eight patients, does not constitute substantial evidence or substantial clinical experience.

In light of these comparisons in this piece, both of which highlight the advantages of Remodulin relating to its route of administration, the fact that Remodulin has not been shown to offer the two principal benefits that Flolan demonstrated is material, and failure to reveal these effectiveness differences in light of the claims implied by the comparison of the products' routes of administration is misleading.

Minimization of Risk

The ad states, "Localized infusion site pain and reaction is a common side effect, but has not been found to be dose related" and "Uncontrolled site pain or reaction management may require the use of an alternate therapy." In addition, the booklet answers the question, "**I heard there is pain associated with Remodulin. How bad is it?,"** by stating:

> Because Remodulin is a prostacyclin molecule and is similar to prostaglandin which is known to cause inflammation, Remodulin can cause local pain where the subcutaneous (in the skin) catheter is placed during or shortly after the infusion starts. However, the severity of pain differs from person to person. Some patients describe it similar to the pain of a tooth ache, others describe it more severely. It should be noted, there have been patients who are not able to tolerate the infusion site pain, no matter what medications or other pain relieving techniques are used. However, there are quite a few patients who have some pain at the start of their therapy but the longer they receive Remodulin, the pain diminishes especially as their PAH symptoms improve and they begin to feel better.

These claims are misleading because they minimize the frequency of <u>severe</u> infusion site pain and reaction. According to the PI, severe infusion site reaction and pain were experienced by 38% and 39% of Remodulin treated patients, respectively. The booklet's characterization of "quite a few" patients suffering initial pain does not reveal how frequently this occurs.

Failure to Submit

These materials were not submitted to FDA on Form FDA 2253 at the time of initial dissemination or initial publication, as required by 21 CFR 314.81(b)(3)(i). Furthermore, these materials were not submitted to FDA 30 days prior to the intended time of initial dissemination or initial publication as required by 21 CFR 314.550.

Failure to Provide Adequate Directions for Use

It appears that the PI was not included with the booklet, in violation of 21 CFR 201.100(d)(1).

Conclusion and Requested Action

The ad and booklet make unsubstantiated effectiveness and comparative claims, omit material facts and minimize risk information, in violation of the Act and FDA's implementing regulations. See 21 U.S.C. 352(a), (n); 321(n); 21 CFR 202.1(e)(5)(i), (iii); (e)(6)(i). In addition, it appears that the PI for Remodulin did not accompany the booklet, as required by 21 CFR 201.100(d), and that these materials were not submitted to FDA as required by 21 CFR 314.81(b)(3)(i) and 21 CFR 314.550.

DDMAC requests that United Therapeutics Corporation immediately cease the dissemination of violative promotional materials for Remodulin such as those described above. Please submit a written response to this letter on or before April 27, 2005, stating whether you intend to comply with this request, listing all violative promotional materials for Remodulin such as those described above, and explaining your plan for discontinuing use of such materials. Because the violations described above are serious, we request, further, that your submission include a comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in this letter to the audience(s) that received the violative promotional materials. Please direct your response to me at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-42, Room 8-B-45, 5600 Fishers Lane, Rockville, MD 20857, facsimile at 301-594-6771. In all future correspondence regarding this matter, please refer to MACMIS ID # 12847 in addition to the NDA number. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Remodulin comply with each applicable requirement of the Act and FDA implementing regulations.

Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

Thomas W. Abrams, R.Ph., MBA
Director
Division of Drug, Marketing, Advertising, and Communications

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/s/

Thomas Abrams
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