IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Horst OLSCHEWSKI et al.
Title:	TREPROSTINIL ADMINISTRATION BY INHALATION
Appl. No.:	13/469,854
Filing Date:	5/11/2012
Examiner:	Sarah Elizabeth Townsley
Art Unit:	1629
Confirmation Number:	9171

AMENDMENT & REPLY UNDER 37 CFR § 1.111

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

This paper responds to the outstanding Non-Final Office Action dated October 3, 2012. Applicants petition for extension of time to make this response timely.

Amendments to the Specification begin on page 2 of this document.

Amendments to the Claims are reflected in the listing of claims which begins on page 3 of this document.

Remarks begin on page 5 of this document.

Amendments to the Specification:

Please amend the specification as follows:

Please replace paragraph 0072 with the following rewritten paragraph:

All inhalations were performed with the OPTINEB® ~~Optineb®~~ ultrasonic nebulizer (Nebutec, Elsenfeld, Germany).

Please replace paragraph 0078 with the following rewritten paragraph:

Study iii) was a randomized, open-label, single blind study. The primary objective was to explore the shortest possible inhalation time for a 15µg dose of inhaled treprostinil. A total of 48 patients inhaled one dose of TRE during right heart catheter investigation. The drug was applied in 18, 9, 3, 2 or 1 breaths. The aerosol was generated by a pulsed ultrasonic nebulizer (VENTA-NEB®, Nebutec, Elsenfeld, Germany) in cycles consisting of 2 seconds aerosol production (pulse) and 4 seconds pause. The device included an opto-acoustical trigger for the patient to synchronize the inspiration to the end of the aerosol pulse, thereby providing exact dosage. The TRE dose of 15µg was either generated during 18 cycles (~~Optineb~~ OPTINEB® filled with 100µg/ml TRE, n=6), 9 cycles (200µg/ml TRE, n=6), 3 cycles (600µg/ml TRE, n=21), 2 cycles (1000µg/ml TRE, n=7) or 1 cycle (2000µg/ml TRE, n=8). Hemodynamics and gas exchange were recorded for 120 - 180 minutes.

Please replace paragraph 0085 with the following rewritten paragraph:

Study iii) was performed with metacresol-free TRE solution, having no specific taste and smell. A total of 48 patients were enrolled. This study aimed at the reduction of inhalation time and aerosol volume needed for pulmonary drug delivery. A modified ~~Optineb~~ OPTINEB® inhalation device was programmed to produce a constant amount of aerosol during repeatable pulses of aerosol generation. With this device, treprostinil could be safely utilized up to a concentration of 2000µg/ml without considerable side effects. No relationship of number or type of side effects to TRE concentration was observed. Reported side effects were mild transient cough (n=6), mild headache (n=2) and mild jaw pain (n=1).

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (original) A pharmaceutical formulation for inhalation comprising an aerosolable solution of treprostinil or a pharmaceutically acceptable salt thereof at a concentration from 500 μg/ml to 2500 μg/ml adapted for use in an ultrasonic nebulizer, wherein the formulation is free of metacresol.

2. (original) The pharmaceutical formulation for inhalation of claim 1, wherein the concentration of treprostinil or its pharmaceutically acceptable salt in the aerosolable solution is 600 μg/ml.

3. (original) The pharmaceutical formulation for inhalation of claim 1, wherein the aerosolable solution has a volume that provides at least one aerosolized dose from 15 μg to 90 μg of treprostinil or a pharmaceutically acceptable salt thereof.

4. (original) The pharmaceutical formulation for inhalation of claim 1, wherein the aerosolable solution has a volume that provides several aerosolized doses sufficient to treat a patient for one day, wherein each dose is from 15 μg to 90 μg of treprostinil or a pharmaceutically acceptable salt thereof.

5. (original) The pharmaceutical formulation for inhalation of claim 4, wherein the concentration of treprostinil or its pharmaceutically acceptable salt in the aerosolable solution is 600 μg/ml.

6. (original) A component for an ultrasonic nebulizer comprising the formulation of claim 1.

7. (original) A component for an ultrasonic nebulizer comprising the formulation of claim 2.

8. (original) A component for an ultrasonic nebulizer comprising the formulation of claim 5.

9. (original) A kit for treating a patient, comprising

(i) an ultrasonic nebulizer (a) adapted to receive a pharmaceutical formulation for inhalation comprising an aerosolable solution of treprostinil or a pharmaceutically acceptable salt thereof at a concentration from 500 µg/ml to 2500 µg/ml, wherein the formulation is free of metacresol and (b) adapted to administer a therapeutically effective single event dose of the formulation comprising from 15 µg to 90 µg of treprostinil or a pharmaceutically acceptable salt thereof by inhalation in 10 or less breaths;

(ii) a pharmaceutical formulation for inhalation comprising an aerosolable solution of treprostinil or a pharmaceutically acceptable salt thereof at a concentration from 500 µg/ml to 2500 µg/ml, wherein the formulation is free of metacresol; and

(iii) instructions for a patient to use the kit to by administering a therapeutically effective single event dose of the formulation comprising from 15 µg to 90 µg of treprostinil or a pharmaceutically acceptable salt thereof by inhalation in 10 or less breaths.

10. (original) The kit of claim 9, wherein the concentration of treprostinil or its pharmaceutically acceptable salt in the aerosolable solution is 600 µg/ml.

11. (original) The kit of claim 9, wherein the ultrasonic nebulizer is adapted to administer a therapeutically effective single event dose of the formulation comprising from 15 µg to 90 µg of treprostinil or a pharmaceutically acceptable salt thereof by inhalation in 3 or less breaths.

12. (original) The kit of claim 9, wherein the ultrasonic nebulizer is adapted to administer a therapeutically effective single event dose of the formulation comprising from 15 µg to 90 µg of treprostinil or a pharmaceutically acceptable salt thereof by inhalation in one breath.

13. (original) The kit of claim 9, wherein the ultrasonic nebulizer is adapted to administer the therapeutically effective single event dose of the formulation as droplets with a diameter less than about 5 microns.

14. (original) The kit of claim 9, wherein the ultrasonic nebulizer is a pulsed ultrasonic nebulizer comprising an opto-acoustical trigger for the patient to synchronize inspiration with an aerosol pulse.

REMARKS

Applicants respectfully request reconsideration and allowance of the present application.

CLAIMS STATUS

Claims 1-14 are pending.

SPECIFICATION

Applicants have amended paragraphs 0072, 0078 and 0085 to address the issue regarding the use of trademarks raised by the PTO on pages 2-3 of the Office Action. No new matter has been added.

CLAIM REJECTIONS UNDER 35 U.S.C. § 103(a)

Claims 1-8 stand rejected as obvious over Chaudry (US Publication no. 2004/0265238). Applicants respectfully traverse.

The PTO failed establish a *prima facie* case of obviousness at least for each of the following independent reasons. Moreover, the unexpected results of a formulation having the particular claimed drug concentration range, which is adapted for use in an ultrasonic nebulizer and which lacks metacresol, would more than rebut any possible case of *prima facie* obviousness.

1) At the time of filing of the presently claimed invention, one of ordinary skill in the art would have been motivated to include metacresol in a treprostinil formulation (notwithstanding that it is not mentioned in Chaudry) because the only FDA-approved and commercially available formulation of treprostinil at that time (for parenteral use) included metacresol (see http://remodulin.com/pdfs/remodulin-prescribinginformation.pdf);[1]

[1] As explained in paragraphs 77-81 of the present specification, the inventors performed two of three initial clinical studies on pulmonary hypertension human patients with a formulation containing metacresol before deciding to conduct a third study in which it was omitted.

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