#17/B
3/12/03

300.1005

UNITED STATES PATENT & TRADEMARK OFFICE

Re:	Application of:	Xiu Xiu Cheng, et al.
	Serial No.:	09/705,630
	Filed:	November 3, 2000
	For:	**Controlled Release Metformin Compositions**
	Examiner: T. Ware	Art Unit: 1615

Assistant Commissioner for Patents
Washington, D.C. 20231

February 24, 2003

AMENDMENT UNDER 37 C.F.R. § 1.111

Sir:

In response to the Office Action mailed on October 22, 2002, Applicants respectfully reconsideration of the application in view of the following amendments and remarks.

IN THE CLAIMS

Please **cancel** claims 2-3, 6, 28, and 31-42 without prejudice.

Please **amend** the claims as follows:

1. (Amended) A controlled release oral dosage form for the reduction of serum glucose levels in human patients with NIDDM, comprising an effective dose of metformin or a pharmaceutically acceptable salt thereof and a controlled-release carrier to control the release of said metformin or pharmaceutically acceptable salt thereof from said dosage form, said dosage form being suitable for providing once-a-day oral administration of the metformin or pharmaceutically acceptable salt thereof, wherein following oral administration of a single dose, the dosage form provides a mean time to maximum plasma concentration (T_{max}) of the metformin from 5.5 to 7.5 hours after administration following dinner.

4. (Amended) The controlled release oral dosage form of claim 1, which provides a mean time to maximum plasma concentration (T_{max}) of metformin at from 6.0 to 7.0 hours after the administration of the dose.

5. (Amended) The controlled release oral dosage form of claim 1, which provides a mean time to maximum plasma concentration (T_{max}) of metformin at from 5.5 to 7.0 hours after the administration of the dose.

7. (Amended) The controlled release oral dosage form of claim 1, which exhibits the following dissolution profiles when tested in a USP type 2 apparatus at 75 rpm in 900 ml of simulated intestinal fluid (pH 7.5 phosphate buffer) and at 37 C:

0-30% of the metformin or salt thereof is released after 2 hours;
10-45% of the metformin or salt thereof is released after 4 hours;
30-90% of metformin or salt thereof is released after 8 hours;
not less than 50% of the metformin or salt thereof is released after 12 hours;
not less than 60% of the metformin or salt thereof is released after 16 hours; and
not less than 70% of the metformin or salt thereof is released after 20 hours.

8. (Amended) The controlled release oral dosage form of claim 1, which exhibits the following dissolution profiles when tested in a USP type 2 apparatus at 75 rpm in 900 ml of simulated intestinal fluid (pH 7.5 phosphate buffer) and at 37 C:

0-25% of the metformin or salt thereof is released after 2 hours;
20-40% of the metformin or salt thereof is released after 4 hours;
45-90% of the metformin or salt thereof is released after 8 hours;
not less than 60% of the metformin or salt thereof is released after 12 hours;
not less than 70% of the metformin or salt thereof is released after 16 hours; and
not less than 80% of the metformin or salt thereof is released after 20 hours.

9. (Amended) The controlled release oral dosage form of claim 1, which provides a width at 50% of the height of a mean plasma concentration/time curve of the metformin from about 4.5 to about 13 hours.

10. (Amended) The controlled release oral dosage form of claim 1, which provides a width at 50% of the height of a mean plasma concentration/time curve of the metformin from about 5.5 to about 10 hours.

11. (Amended) The controlled release oral dosage form of claim 1, which provides a mean maximum plasma concentration (C_{max}) of metformin which is more than about 7 times the mean plasma level of said metformin at about 24 hours after the administration.

12. (Amended) The controlled release oral dosage form of claim 1, which provides a mean maximum plasma concentration (C_{max}) of metformin which is from about 7 times to about 14 times the plasma level of said metformin at about 24 hours after administration.

13. (Amended) The controlled release oral dosage form of claim 1 which provides a mean maximum plasma concentration (C_{max}) of metformin which is from about 8 times to about 12 times the plasma level of said metformin at about 24 hours after administration.

14. (Amended) The controlled release oral dosage form of claim 1 which provides a mean maximum plasma concentration (C_{max}) of metformin from about 1500 ng/ml to about 3000 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin.

15. (Amended) The controlled release oral dosage form of claim 1, which provides a mean maximum plasma concentration (C_{max}) of metformin from about 1700 ng/ml to about 2000 ng/ml, based on administration of a 2000 mg once-a-day dose of metformin.

16. (Amended) The controlled release oral dosage form of claim 1 which provides a mean AUC_{0-24hr} of at least 80% of the mean AUC_{0-24} provided by administration of an immediate release reference standard twice a day, wherein the daily dose of the reference standard is substantially equal to the once-a-day dose of metformin administered in the controlled release dosage form.

14. (Amended) The controlled release oral dosage form of claim 1 which provides a mean $AUC_{0\text{-}24hr}$ of at least 90% of the mean $AUC_{0\text{-}24}$ provided by administration of an immediate release reference standard twice a day, wherein the daily dose of the reference standard is substantially equal to the once-a-day dose of metformin administered in the controlled release oral dosage form.

B3 cont'd

15. (Amended) The controlled release oral dosage form of claim 1 which provides a mean $AUC_{0\text{-}24hr}$ from about 17200 ng.hr/ml to about 33900 ng.hr/ml, based on administration of a 2000 mg once-a-day dose of metformin.

16. (Amended) The controlled release oral dosage form of claim 1 which provides a mean $AUC_{0\text{-}24hr}$ from about 17200 ng.hr/ml to about 26500 ng.hr/ml, based on administration of a 2000 mg once-a-day dose of metformin.

17. (Amended) The controlled release oral dosage form of claim 1 which provides a mean $AUC_{0\text{-}24hr}$ from about19800 ng.hr/ml to about 33900 ng.hr/ml, based on administration of a 2000 mg once-a-day dose of metformin.

18. (Amended) The controlled release oral dosage form of claim 1 which provides a mean $AUC_{0\text{-}\infty}$ of 18277 ± 2961 ng·hr/ml and a mean C_{max} of 1929 ± 333 ng/ml, for administration of a 1700 mg once-a-day dose of metformin after an evening meal.

19. (Amended) The controlled release oral dosage form of claim 1 which provides a mean $AUC_{0\text{-}\infty}$ of 20335 ± 4360 ng·hr/ml and a mean C_{max} of from 2053 ± 447 ng/ml, for administration of a 2000 mg once-a-day dose of metformin after an evening meal.

20. (Amended) The controlled release oral dosage form of claim 1 which provides a mean $AUC_{0\text{-}24}$ of 26818 ± 7052 ng·hr/ml and a mean C_{max} of 2849 ± 797 ng/ml, for administration of a 2000 mg once-a-day dose of metformin after an evening meal.

(Amended) The controlled release oral dosage form of claim 1 which provides a mean AUC_{0-24} of 22590 ± 3626 ng·hr/ml and a mean C_{max} of 2435 ± 630 ng/ml on the first day of administration and a mean AUC_{0-24} of 24136 ± 7996 ng·hr/ml and a mean C_{max} of 2288 ± 736 ng/ml on the 14th day of administration, for [based on] administration of a 2000 mg once-a-day dose of metformin after an evening meal.

(Amended) The controlled release oral dosage form of claim 17 which provides a mean $t_{1/2}$ from 2.8 to 4.4.

(Amended) The controlled release oral dosage form of claim 9, which provides a mean time to maximum plasma concentration (Tmax) of metformin from 5.5 to 7.0 hours after administration.

(Amended) The controlled release dosage form of claim 1, wherein the metformin or pharmaceutically acceptable salt thereof is provided by at least one controlled-release tablet, said tablet comprising:

(a) a core comprising:
  (i) the metformin or a pharmaceutically acceptable salt;
  (ii) optionally a binding agent; and
  (iii) optionally an absorption enhancer;
(b) a membrane coating surrounding the core; and
(c) at least one passageway in the membrane.

REMARKS

Reconsideration of the present application is respectfully requested. An early and favorable action on the merits is earnestly solicited.

1. **Status of the Claims**

Claims 1, 4-5, 7-30 are pending; claims 2-3, 6, and 31-42 have been cancelled without prejudice; and claims 1 and 4-5, 7-25, 27 and 29 have been amended without prejudice. It is respectfully submitted that no new matter has been added by virtue of this amendment.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.