Docket No.: 0020-5041PUS2
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Mitsutaka NAKAMURA et al.

Application No.: 10/525,021 | Confirmation No.: 3141

Filed: February 18, 2007 | Art Unit: 1612

For: AGENT FOR TREATMENT OF SCHIZOPHRENIA | Examiner: MAEWALL, S.

AMENDMENT IN RESPONSE TO FINAL OFFICE ACTION AND RCE

MS AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Madam:

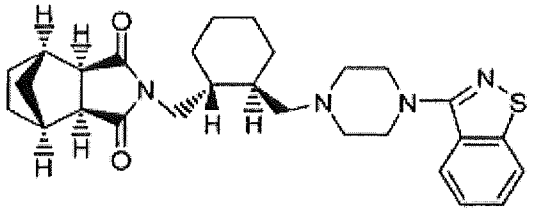
In response to the Office Action issued on September 17, 2008, the following amendments and remarks are respectfully submitted in connection with the above-identified application:

Amendments to the claims begin on **page 2** of this paper;

Remarks begin on **page 4** of this paper; and

AMENDMENTS TO THE CLAIMS

1. **(Currently Amended)** A method for treating schizophrenia in a patient suffering from schizophrenia, without said treatment being accompanied by any extrapyramidal symptoms, which comprises orally administering a once daily dose of 5 mg to 120 mg of the active compound: (1R,2S,3R,4S)-N-[(1R,2R)-2-[4-(1,2-benzoisothiazol-3-yl)-1-piperazinylmethyl]-1--cyclohexylmethyl]-2,3-bicyclo[2.2.1]heptanedicarboxyimide of the formula (1):



(1)

or a pharmaceutically acceptable salt thereof to a patient suffering from schizophrenia, wherein the administration of said active compound improves ~~the positive symptoms of schizophrenia and/or~~ the negative symptoms of schizophrenia and/or the cognitive dysfunction of schizophrenia.

2. **(Previously Presented)** The method of claim 1, wherein the pharmaceutically acceptable salt of said active compound is (1R,2S,3R,4S)-N-[(1R,2R)-2-[4-(1,2-benzoisothiazol-3-yl)-1-piperazinylmethyl]-1-cyclohexylmethyl]-2,3-bicyclo[2.2.1]heptanedicarboxyimide hydrochloride.

3. – 4. **(Canceled)**

5. **(Previously Presented)** The method of claim 1 or claim 2, wherein 20 mg to 80 mg of said active compound is administered to said patient.

6. – 7. **(Canceled)**

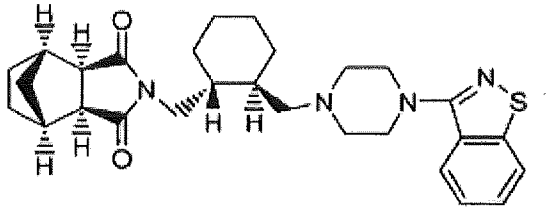
8. **(Previously Presented)** The method of claim 1 or claim 2, wherein said patient is in a chronic stage of schizophrenia, and wherein 20 mg to 80 mg of said active compound is administered to said patient.

9. – 10. **(Canceled)**

11. **(Previously Presented)** The method of claim 8, wherein 50 mg to 80 mg of said active compound is administered to said patient.

12. – 19. **(Canceled)**

20. **(Previously Presented)** A method for treating the positive symptoms and the negative symptoms of schizophrenia in a patient suffering from schizophrenia which comprises orally administering to said patient a preparation comprising a single active compound or a pharmaceutically acceptable salt of said active compound, wherein 5 mg to 120 mg of said active compound is administered once a day to said patient, and wherein said active compound is (1R,2S,3R,4S)-N-[(1R,2R)-2-[4-(1,2-benzoisothiazol-3-yl)-1-piperazinylmethyl]-1-cyclohexylmethyl]-2,3-bicyclo[2.2.1]heptanedicarboxyimide of the formula (1):



(1)

21. **(Cancelled)**

REMARKS

Status of the Claims

Claims 1-2, 5 and 8, 11, and 20-21 are pending.

Claim 1 has been amended to incorporate claim 21.

Claim 21 has been cancelled.

No new matter has been added.

1. Claim Rejections under 35 USC Section 103

On pages 3-5 of the Office Action, the Examiner rejects claims 1-13 as allegedly obvious over Somerville et al. (W0 03/066039) in view of Wong et al. (USPN 6,964,962) and Saji et al., U.S. Patent 5,532,372). Applicants respectfully traverse.

1.1 The references do not make obvious the claimed dose range.

As a preliminary matter, Applicants note that the Examiner has found it necessary to add an additional reference to the obviousness rejection. The Examiner has already admitted that Sommerville does not disclose a particular dose of SM-13496. (Office Action page 3, lines 10-11). The Examiner also admits that Wong et al. "teach [a] wide range of dosage." (*Id.* at line 17). Consequently, Applicants submit that the Examiner has recognized that the previous obviousness rejection was deficient, at least because it did not disclose the dosage as claimed in the present application.[1]

[1] To ensure the record is complete, Applicants reiterate that Wong, in combination with Sommerville, does not render the present invention obvious because Wong teaches a broad dosing of SM-13496 *in combination* with a norepinephrine reuptake inhibitor, and that the dose range for SM-13496 would either not be effective, or would not be tolerated by a patient. (See Amendment dated June 17, 2008, page 7-9).

The Examiner cites Saji for teaching "oral preparations of the claimed compound containing 10 mg, 20 mg, or 40 mg of a hydrochloride of formula 1." (Office Action, page 3). The Examiner further argues, "when the difference between the claimed invention and the prior art is the range or value of a particular variable, then a prima facie rejection is properly established when the difference in the range or value is minor." *In re Geisler*, 43 USPQ2d 1362, 1365 (Fed. Cir. 1997), *quoting Haynes Int'l, Inc. v. Jessop Steel Co.,* 28 USPQ2d 1652, 1655 n.3 (Fed. Cir. 1993).

Applicants submit that Saji does not remedy the deficiencies of the combination of Wong and Sommerville to establish *prima facie* obviousness because the difference between the range is not minor. Saji discloses an *extremely* broad range of compounds (almost 200 compounds), which it claims have "significant" anti-psychotic activity (See col. 12, lines 25-28; and col. 2 lines 9-15 and 64-65). In contrast to the Examiner's assertions, Saji discloses that *any one* of this broad range of compounds could be administered in "a dose of from about 1 to 1,000 mg, preferably from about 5 to 100 mg, in case of oral administration and at a daily dose of from about 0.1 to 1000 mg, preferably from about 0.3 to 50 mg, in case of intravenous injection." (Saji, col. 12, lines 19-23). Furthermore, the *in vivo* methods disclosed in Saji merely disclose "a designated amount of the test compound is orally administered." (Saji, col. 13, lines 30-31). Thus, Applicants submit that one of skill would not be able to determine which particular compound would be effective at any particular dose range from the disclosure in Saji.

Moreover, Applicants submit that the dosage of Saji does not speak to efficacy against the negative symptoms of schizophrenia. Saji is directed to a an "anti-psychotic" drug, which may be effective against "schizophrenia, senile insanity, manic-depressive psychosis, neurosis, etc.." (Saji, col. 1, line10-12). Saji does not disclose that this compound can be used for treatment of the negative symptoms of schizophrenia and/or the cognitive dysfunction of schizophrenia. Moreover, at the time of filing, treatment of the negative symptoms using an atypical neuroleptic for schizophrenia which did not have adverse side effects was not recognized except by the inventors. (See Amendment dated July 16, 2008, page 10).

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