

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Brian Ault, <i>et al.</i>	Filed: September 3, 2009
Application No: 12/553,107	Attorney Docket No: 103526-US
Examiner: Gina Chieun Yu Justice	Confirmation No. 5949
Art Unit: 1617	
Title: Method for Delivering a Pharmaceutical Composition to Patient in Need Thereof	

Commissioner for Patents
PO Box 1450
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January 30, 2013

AMENDMENT C AND RESPONSE TO FINAL OFFICE ACTION

This amendment is being filed with an RCE in response to the July 30, 2012 final Office action in the above-referenced patent application.

Claim amendments begin on page **2**.

Remarks begin on page **5**.

Claim Amendments

Please amend the claims as follows:

Claims 1-18 (cancelled).

19. **(previously presented)** A method for treating osteoarthritis, rheumatoid arthritis, or ankylosing spondylitis comprising orally administering to a patient in need thereof an AM unit dose form and, 10 hours ($\pm 20\%$) later, a PM unit dose form, wherein:

the AM and PM unit dose forms each comprises:

naproxen, or a pharmaceutically acceptable salt thereof, in an amount to provide 500 mg of naproxen, and

esomeprazole, or a pharmaceutically acceptable salt thereof, in an amount to provide 20 mg of esomeprazole;

said esomeprazole, or pharmaceutically acceptable salt thereof, is released from said AM and PM unit dose forms at a pH of 0 or greater,

the AM and PM unit dose forms target:

i) a pharmacokinetic (pk) profile for naproxen where:

a) for the AM dose of naproxen, the mean $C_{\max}$ is 86.2 $\mu\text{g/mL}$ ($\pm 20\%$) and the median $T_{\max}$ is 3.0 hours ($\pm 20\%$); and

b) for the PM dose of naproxen, the mean $C_{\max}$ is 76.8 $\mu\text{g/mL}$ ($\pm 20\%$) and the median $T_{\max}$ is 10 hours ($\pm 20\%$); and

ii) a pharmacokinetic (pk) profile for esomeprazole where:

a) for the AM dose of esomeprazole, the mean area under the plasma concentration-time curve from when the AM dose is administered to 10 hours ($\pm 20\%$) after the AM dose is administered ($\text{AUC}_{0-10,\text{am}}$) is 1216 $\text{hr} \cdot \mu\text{g/mL}$ ($\pm 20\%$),

b) for the PM dose of esomeprazole, the mean area under the plasma concentration-time curve from when the PM dose is administered to 14 hours ($\pm 20\%$) after the PM dose is administered ($\text{AUC}_{0-14,\text{pm}}$) is 919 $\text{hr} \cdot \mu\text{g/mL}$ ($\pm 20\%$), and

c) the total mean area under the plasma concentration-time curve for esomeprazole from when the AM dose is administered to 24 hours

($\pm 20\%$) after the AM dose is administered (AUC_{0-24}) is 2000
hr* $\mu\text{g/mL}$ ($\pm 20\%$); and.

the AM and PM unit dose forms further target a mean % time at which intragastric pH remains at about 4.0 or greater for about a 24 hour period after reaching steady state that is at least about 60%.

Claims 20-28 (cancelled).

29. **(previously presented)** The method according to claim 19, wherein the mean % time at which intragastric pH remains at about 4.0 or greater for about a 24 hour period after reaching steady state is at least about 71%.

Claims 30-32 (cancelled).

33. **(previously presented)** The method according to claim 19, wherein said AM and PM unit dose forms are administered for a period of at least about 6 days.

34. **(previously presented)** The method according to claim 19, wherein said AM and PM unit dose forms are administered for a period of at least about 9 days.

Claims 35-39 (cancelled).

40. **(currently amended)** The method according to claim 19, wherein said AM and PM unit dose forms are each a multilayer tablet comprising at least one core and at least a first layer and a second layer, wherein:

- i) said core comprises naproxen, or pharmaceutically acceptable salt thereof;
- ii) said first layer is a coating that at least begins to release the naproxen, or pharmaceutically acceptable salt thereof, when the pH of the surrounding medium is about 3.5 or greater; and
- iii) said second layer comprises esomeprazole or a pharmaceutically acceptable salt thereof, wherein said esomeprazole or **pharmaceutically acceptable** salt thereof is released at a pH of from 0 or greater.

Claim 41 (cancelled).

42. **(currently amended)** The method according to claim 40, wherein said esomeprazole or **pharmaceutically acceptable** salt thereof is released at a pH of from 0 to about 2.

Claims 43 and 44 (cancelled).

45. **(previously presented)** The method according to claim 40, wherein said multi-layer tablet is substantially free of sodium bicarbonate.

Claims 46 and 47 (cancelled).

Remarks/Arguments

Applicants request reconsideration of this application on the merits.

I. Claim amendments

Claims 19, 29, 33, 34, 40, 42, and 45 are pending. Applicants have amended claims 40 and 42 to characterize the recited salt as “pharmaceutically acceptable.” This makes claims 40 and 42 more consistent with claim 19, *i.e.*, the claim from which claims 40 and 42 ultimately depend.

Applicants continue to reserve their right to pursue any subject matter cancelled or otherwise disclosed in this application in or more later-filed continuations and/or divisionals.

II. Response to obviousness-type double-patenting rejection

Claims 19, 29, 33, 34, 40, 42, and 45 have been rejected as obviousness-type double-patenting over claims 1-55 of Plachetka (U.S. Patent No. 6,926,907). Applicants request withdrawal of this rejection.

Applicants respectfully submit that claims 19, 29, 33, 34, 40, 42, and 45 are patentably distinct over Plachetka’s claims 1-55 for reasons analogous to those discussed below regarding the non-obviousness of claims 19, 29, 33, 34, 40, 42, and 45 over Plachetka generally. On this ground alone, Applicants submit this rejection should be withdrawn on the merits.

In addition, Applicants respectfully submit that this rejection is not ripe until at least one of the rejected claims has been found to be otherwise patentable. Accordingly, to the extent this rejection is not withdrawn on the merits, Applicants request that it be held in abeyance until there is at least one claim in this application found to be otherwise allowable.

III. Response to rejection under 35 U.S.C. §103(a)

Claims 19, 29, 33, 34, 30, 42, and 45 have been rejected as being obvious over Plachetka. Applicants request withdrawal of this rejection.

A. Claim 19

Applicants respectfully submit that claim 19 represents a non-obvious selection over Plachetka. This selection is characterized by unexpected results. Nothing in Plachetka would have suggested such unexpected results at the time of Applicants’ filing.

Claim 19 recites multiple selections over Plachetka, which include:

- (1) the use of the specific combination of naproxen and esomeprazole;
- (2) the specific combined doses of naproxen (*i.e.*, 500 mg/unit dose) and esomeprazole (*i.e.*, 20 mg/unit dose); and
- (3) the administration of the above combination in an AM unit dose form, and, 10 hours ($\pm 20\%$) later, a PM unit dose form.

Plachetka fails to teach or suggest any one these specific selections or the combination thereof.

The Combination of Naproxen and Esomeprazole

Applicants selected one NSAID, naproxen, from the many possible NSAIDs mentioned in Plachetka. *See, e.g.*, Plachetka, col. 5, line 20 to col. 6, line 67 (naproxen is merely one of 26 specific NSAIDs mentioned). Applicants further selected one acid inhibitor, esomeprazole, from the many acid inhibitors mentioned in Plachetka. These include two general categories (H₂ blockers and proton pump inhibitors), and esomeprazole is merely one of the eleven example acid inhibitors Plachetka mentions. *See e.g.*, Plachetka, col. 7, lines 1-18.

Although Plachetka does mention both naproxen and esomeprazole, Plachetka places no particular emphasis on the specific combination of the two. Nor does Plachetka describe any formulation or *in vitro* or *in vivo* experiments using such a combination. Thus, a skilled artisan, when reading Plachetka, would have had no guidance or motivation to specifically select the combination of naproxen and esomeprazole, when confronted with hundreds of possible combinations Plachetka presents. Nor would the skilled artisan have had any expectation that the combination of naproxen and esomeprazole, as currently recited in claim 19, would produce Applicants' unexpected pharmacodynamic profile (*see below*).

500 mg of Naproxen Combined with 20 mg Esomeprazole per Unit Dose

Claim 19 recites a selection of a combination of 500 mg of naproxen with 20 mg of esomeprazole for each unit dose form. Plachetka fails to specifically teach or suggest these doses when these ingredients are used in combination with each other. In fact, Plachetka, while mentioning various dosage ranges for naproxen and esomeprazole, provides that 550 mg/unit dose is generally preferred for naproxen and 40 mg/unit dose is generally preferred for esomeprazole. *See, e.g.*, Plachetka, col. 6, lines 6-11 and col. 7, lines 12-13.

Consequently, a skilled artisan reading Plachetka, even if choosing naproxen and/or esomeprazole, would have had no guidance or motivation to specifically select Applicants' recited combined doses for naproxen and esomeprazole, particularly when confronted with the many choices of doses for the various drugs Plachetka mentions.

*Administering the Above Combination in
an AM Unit Dose Form and, 10 hours ($\pm 20\%$) Later, a PM Unit Dose Form*

Claim 19 recites administering the combination, 500 mg of naproxen and 20 mg of esomeprazole, in an AM unit dose form and, 10 hours ($\pm 20\%$) later, a PM unit dose form. Plachetka fails to specifically teach or suggest such a treatment regime. Plachetka does discuss twice-daily treatment (*see, e.g.*, Plachetka, Example 9). But nowhere does Plachetka specifically discuss when each of the two doses should be administered, or at what time interval. Thus, a skilled artisan reading Plachetka, even if selecting a twice-daily treatment regime, would not have had any specific guidance or motivation to select Applicants' recited treatment regime.

Lack of Prima Facie Case / Presence of Unexpected Results

To establish a *prima facie* case of obviousness, some reason must be identified that would have led a skilled artisan to pursue a claimed species. *See Yamanouchi Pharm. Co. Ltd. V. Danbury Pharmacol., Inc.*, 231 F.3d 1339, 1344 (Fed. Cir. 2000) (holding that to establish a *prima facie* case of obviousness post-KSR, there must be a showing that those of skill in the art would have had motivation to pursue the claimed species); *see also Takeda Chem. Indus. v. Alphapharm Pty, Ltd.*, 492 F.3d 1350, 1356 (Fed. Cir. 2007). Plachetka fails to meet this requirement because it fails to specifically teach or suggest any of the above three selections, much less Applicants' recited combination thereof.

Against this backdrop, Applicants further point out that they have unexpectedly discovered and demonstrated that, by practicing the recited method, they can achieve a pharmacodynamic profile in which the mean % of time for which a patient's intragastric pH remains at about 4.0 or greater for about 24 hours after reaching steady state is at least about 60%. More specifically, in a 9-day clinical study, they achieved a pharmacodynamic profile in which the mean % time of intragastric pH at above 4.0 over 24 hours was about 71.35%. *See, e.g.*, Specification, page 41, Table 4. By contrast, among the tested formulations in Plachetka, the combination of 40 mg of famotidine with 550 mg of naproxen maintained the intragastric pH at greater than 4.0 for only 49% of the time during the 8-10 hours following

naproxen sodium dosing. *See* Plachetka, col. 19, Example 9. Applicants submit that a skilled artisan would readily correlate the extended pH > 4.0 period produced by Applicants' method with desired reduced gastrointestinal risk associated with stomach acid secretion.

Plachetka fails to specifically teach or suggest that the beneficial pharmacodynamic profile observed with Applicants' method could be obtained when (1) using esomeprazole with naproxen, (2) using the specific dosages of 20 mg/unit esomeprazole with 550 mg/unit dose naproxen, and (3) following a treatment regimen that comprises a PM dose administered 10 hours ($\pm 20\%$) after an AM dose. Thus, a skilled artisan reading Plachetka would not have expected the beneficial results of Applicants' method, specifically the post-administration intragastric pH > 4.0 period discussed above.

Inherency

The obviousness rejection appears to be based on a conclusion that Applicants' pharmacokinetic and pharmacodynamics profiles are inherent results of administering the formulation according to Plachetka's teachings twice per day, and, as such, are not evidence of inventiveness. *See* page 8 of the Office action. Applicants respectfully traverse --- this reliance on inherency is improper.

At the outset, while inherency may apply to anticipation determinations, it has only very limited application in the context of obviousness. And the Courts have often balked at basing an obviousness finding on an *unknown* inherent property present in the prior art. *See Trintec Indus., Inc. v. TOP-U.S.A. Corp.*, 295 F.3d 1292, 1296 (Fed. Cir. 2002) ("obviousness is not inherent anticipation"); *In re Rijckaert*, 9 F.3d 1531, 1534 (Fed. Cir. 1993) ("Such a retrospective view of inherency is not a substitute for some teaching or suggestion supporting an obviousness rejection."). *See also, In re Spormann*, 363 F.2d 444, 448 (C.C.P.A. 1966) ("That which may be inherent is not necessarily known."). This makes sense. After all, the suggestion to combine or modify prior art must occur before an Applicant's date of invention. If an inherent property is unknown at the time, it obviously cannot provide such a suggestion. *See, In re Rijckaert*, 9 F.3d at 1534.

Moreover, the use of inherency in the instant rejection is wholly misplaced because the inherency is being used to characterize the unexpected results of the claimed method. More specifically, the Office action concedes that Plachetka fails to specifically disclose the particular combination of operative elements recited in claim 19. The Office action, however, justifies the obviousness rejection by asserting that the unexpected results of the combination

are inherent from the combination. Applicants are unaware of any law allowing this type of reasoning. Inherency cannot be used, as it has here, to disregard the unexpected results of a novel combination of operative elements.

Simply put, Plachetka fails to specifically teach or suggest the novel selections of Applicants' method. And Plachetka fails to predict the unexpected results of Applicants' claimed method, particularly the above-described percentage of time over which the intragastric pH is maintained at 4.0 or above. Accordingly, Applicants respectfully submit that Plachetka fails to render claim 19 obvious.

B. Claims 29, 33, 34, 40, 42, and 45

Claims 29, 33, 34, 40, 42, and 45 depend directly or indirectly from claim 19. Thus, they too are necessarily patentable over Plachetka for at least the same reasons as claim 19.

* * * * *

Applicants request a three-month extension to respond to the July 30, 2012 final Office action, and authorize the Commissioner to charge the corresponding fee to Deposit Account No. **260166**. If any other fee(s) is due in connection with this filing, Applicants authorize the Commissioner to charge the fee(s) to Deposit Account No. **260166** (referencing Attorney Docket No. **103526-US**). In addition, if there is ever any other fee deficiency or overpayment under 37 C.F.R. §1.16 or 1.17 in connection with this patent application, the Commissioner is hereby authorized to charge such deficiency or overpayment to Deposit Account No. **260166** (referencing Attorney Docket No. **103526-US**).

Applicants submit the pending claims are in condition for allowance, and request this application be allowed. The Examiner is requested to call the Undersigned if any issues arise that can be addressed over the phone to expedite examination.

Amendment C and Response to Final Office Action
Appl. No. 12/553,107
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