

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Brian Ault, <i>et al.</i>	Filed: September 3, 2009
Application No: 12/553,107	Attorney Docket No: POZN.P0026US
Examiner: Gina C. Yu Justice	Confirmation No. 5949
Title: Method for Delivering a Pharmaceutical Composition to Patient in Need Thereof	

<p>CERTIFICATE OF ELECTRONIC TRANSMISSION</p> <p>I hereby certify that this correspondence is being electronically filed with the United States Patent and Trademark Office via EFS-Web on the date below:</p> <p>September 25, 2015 /Steven L. Highlander/ Date Steven L. Highlander</p>

RESPONSE TO FINAL OFFICE ACTION MAILED MARCH 26, 2015

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Commissioner:

This is in response to the Office Action (“Action”) mailed on March 26, 2015, to which a response is due on September 26, 2015, by virtue of the accompanying Petition for Extension of Time (3 months) and payment of fees. No other fees are believed due in connection with this response; however, should applicants payment be missing, or any other fees due, the Commissioner is authorized to debit Parker Highlander PLLC Deposit Acct. No. 50-5902/POZN.P0026US/SLH.

A **Listing of Claims** begins on page 2 of this response; **Remarks** begin on page 5.

LISTING OF CLAIMS

The following listing of claims replaces all previous listings or versions thereof:

1-18. (Canceled)

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%.

20-28. (Canceled)

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%.

30-32. (Canceled).

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.

35-39. (Canceled)

40. (Previously presented) 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.

41. (Canceled)

42. (Previously presented) 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.

43-44. (Canceled)

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

46-47. (Canceled)

REMARKS

I. Status of the claims

Claims 19, 29, 33, 34, 40, 42 and 45 are pending in the application and stand rejected under 35 U.S.C. §103 and for obviousness-type double-patenting. The specific grounds for rejection, and applicants' response thereto, are set out in detail below.

II. Rejection under 35 U.S.C. §103

Claims 19, 29, 33, 34, 40, 42, and 45 are rejected over Hassan-Alin *et al.* in view of Plachetka (U.S. Patent 6,926,907). Applicants traverse.

Hassan-Alin is cited as teaching that there are no drug-drug interactions between esomeprazole and naproxen, as demonstrated by a study in human subjects. In addition, the reference indicates that esomeprazole is expected to be more effective than other PPI's against NSAID-associated ulcers and to provide GI protection. Plachetka is cited as teaching a coordinated delivery of NSAIDS, including naproxen, with an acid inhibitor. From this, the examiner argues that use of esomeprazole in combination with naproxen, using an AM-PM dosing regimen, would be obvious.

To establish *prima facie* obviousness of a claimed invention, all the claim features must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). Indeed, all words in a claim must be considered in judging the patentability of that claim against the prior art. *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). Once again, the examiner has not addressed at least the following highlighted claim features:

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

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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 ($AUC_{0-10,am}$) 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 ($AUC_{0-14,pm}$) 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 $\text{hr} \cdot \mu\text{g/mL}$ ($\pm 20\%$); 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%.

There simply is no question, on the record, that the cited art lacks any teaching or suggestion of these features.

Applicants begin by directing the examiner to the decision in *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litigation* (Fed. Cir. 2012), the facts and holding of which are relevant to the instant application. There, the Federal Circuit concluded that the district court's determination of obviousness was in error because the district court failed to consider the *lack of a known pharmacokinetic (pK)/pharmacodynamics (pD)*

relationship for the claimed drug formulation.¹ The same arguments apply to the instant application.

In *In re Cyclobenzaprine*, the Federal Circuit criticized the district court in its improper assumption of bioequivalence between immediate release and extended release drug forms. Here, the examiner similarly argues expected equivalence between immediate release esomeprazole (present claims) and extended release esomeprazole (Hassan-Alin), which as shown in the present specification, is not supported by the data.² Key in this aspect of the Federal Circuit's holding was that cyclobenzaprine "lacked a **known** pK/pD relationship at the time of invention," which the Federal Circuit believed was critically important because "[w]ithout such a **known** relationship [], skilled artisans could not predict whether any particular pK profile, including a bioequivalent one, would produce a therapeutically effective formulation" (emphasis added).

Likewise, in the instant application, claim 19 focuses on esomeprazole and naproxen pharmacokinetic ("pK") profiles (see Applicants' specification, pp. 43-53), and the pharmacodynamic ("pD") endpoint wherein the mean % of time for which the patient's intragastric pH remains at about 4.0 or greater for about 24 hours after reaching steady state is at least about 60% (see Applicant's specification, Table 4, p. 41 (mean % time of pH >4.0 = 71.35 (SD = 13.01))), for PN400/E20 (having **immediate release esomeprazole**) in Example 1. These profiles and endpoint were not a "**known** pK/pD relationship at the time of invention," and in fact were unexpected and surprising in light of the data also found in Applicants' specification showing significantly different results for EC E20+naproxen (having **extended release esomeprazole**), as shown at least by the following results:

¹ In particular, the court focused on the pharmacokinetic values in claim 3.

² See discussion of Hassan-Alin *et al.*, 2005 in Section II(A), below, regarding this point.

- “On Day 9, ... PN400/E20 treatments resulted in a greater percent time with intragastric pH>4.0 than treatment with EC E20 + naproxen” (Applicants’ specification, p. 41 and see Table 4);
- “By Day 9, however, the esomeprazole AUC₀₋₁₀ for the PN400/E20 treatment group was greater than the EC E20 + naproxen treatment group (1216 vs 1046 hr·ng/mL, respectively) and C_{max,am} from the PN400/E20 treatment group was almost double that of the EC E20+naproxen treatment group (715 vs 435 ng/mL, respectively).” (Applicants specification, p. 47);
- “Repeat doses of PN 400/E30 and PN 400/E20 resulted in faster onset of increased intragastric pH (at about 1 hour post dose) than EC E20 + naproxen, which was at about 1.5 hours post-dose (Figure 1). As shown in the Figure 8A, the release of naproxen from PN 400 occurred 1.5 to 2 hours post AM dose. Before naproxen was absorbed to peak concentrations following PN 400 treatment, intragastric pH had already achieved high levels, well above pH 4.0 (Figure 8A). In fact, with the BID regimen of PN 400/E20, given 1 hour before a meal, the intragastric pH was maintained at above 4.0 for greater than 70% of time over a 24-hour period, which would encompass any rise in plasma naproxen concentrations throughout the day. In contrast, EC E20 + naproxen produced peak naproxen concentrations that preceded the increase in intragastric pH (Figure 8B). In fact, peak naproxen concentrations occurred 1 to 2 hours post dose, which coincided with the time period when intragastric pH was lowest.” (Applicants’ specification, p. 54).

This extended period of pH at 4.0 or greater provided by PN400/E20 (having *immediate release esomeprazole*) over EC E20+naproxen (having *extended release esomeprazole*) is believed to be advantageous toward protecting patients from adverse effects of naproxen, and is a surprising and unexpected result given that this difference is maintained over an extended

period of time even though both formulations include esomeprazole, which as the examiner asserts, was known to provide “more time with intragastric pH>4 than other proton pump inhibitors.” See Action at page 3. Therefore, as shown above, it is improper for the examiner to assume bioequivalence between immediate release and extended release esomeprazole drug forms (just as the district court did in *In re Cyclobenzaprine*, before being reversed by the Federal Circuit).

In *In re Cyclobenzaprine*, the Federal Circuit also distinguished its findings over *KSR Int'l Co. v. Teleflex Inc.*, quoting that opinion for the proposition that an invention is obvious when the skilled worker pursues “*known* options” from “a finite number of identified, predictable solutions” (emphasis added). The Federal Circuit went on to analogize the district court's opinion with the Federal Circuit's language in *In re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir. 2009) as an improper obviousness analysis that is really hindsight reconstruction: when a defendant is “‘merely throw[ing] metaphorical darts at a board’ in hopes of arriving at a successful result,” and “the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful,” this is not obviousness but hindsight reconstruction.

In summary, on facts very similar to those presented here, the USPTO's reviewing court struck down a comparable finding of unpatentability on the grounds that the prior art's general guidance was insufficient to render a claim obvious where that claim recited specific pK/pD parameters that were nowhere present in the art, nor could they be selected from a “finite” number of options readily apparent to those of skill in the art. As such, there is no justification for holding that the presently claimed subject matter was reasonably suggested by Hassan-Alin, even when taken in view of Plachetka.

A. Enteric Coating

Applicants previously asserted that it was almost certain that the esomeprazole used by Hassan-Alin was enterically-coated. Thus, any attempted extrapolation from this material to the pharmacokinetic profile of esomeprazole of the present claims is completely inappropriate due to the fact that the esomeprazole used to generate the data that is embodied in the present claims was *not* enterically-coated. This provides yet another reason that the skilled artisan could not have envisioned, nor expected to succeed with, the presently claimed subject matter.

The examiner argues that Applicants have presented no evidence that the form of esomeprazole in Hassan-Alin is enterically-coated. As a preliminary matter, it should be noted that it is the examiner's burden, not Applicants', to establish that the cited art is in fact relevant to the claimed subject matter, *as well as how*. Here all Applicants need to do is point out there is no evidence of record that Hassan-Alin's esomeprazole was *not* enteric coated (which was the state of the art at the time of publication), and the rejection is rebutted. Simply put, Applicants need not disprove that which has not been proven.

Nevertheless, in the interest of advancing prosecution, Applicants provide the following additional information. In 2005, in what was undoubtedly the follow up publication to the presently cited reference, Hassan-Alin *et al.* stated in "Lack of Pharmacokinetic Interaction between Esomeprazole and the Nonsteroidal Anti-Inflammatory Drugs Naproxen and Rofecoxib in Healthy Subjects," *Clin. Drug. Invest.* 25(11):731-740, that their patients took Nexium®, AstraZeneca Tablet Production, Sweden, which is well known to be enterically-coated. Notably, that paper further provides a very different pK/pD profile than the pending claims, thereby completely undercutting the examiner's argument that one could necessarily achieve the same result if following Hassan-Alin's 2003 teachings.

B. Inherency

Without explicitly invoking the doctrine, the examiner attempts to sweep away the fact that the cited references provide none of the preceding claim recitations by resorting to an inherency theory, noting that “the resulting pharmacokinetics necessarily flow from such [an] obvious administration method.” As will be explained below, the examiner is applying inherency in a way that cannot be supported by the relevant legal precedent.

Even assuming the examiner’s characterization of the art to be correct – something that is conceded only for the purpose of the following argument – the claims are nonetheless patentable. The critical mistake arises in the examiner’s implicit assertion that inherency can address the limitations of applicants’ claims that are missing from the art. The topic of inherency, in the context of obviousness, is discussed in MPEP § 2141, the relevant portion of which is reproduced below:

In determining whether the invention as a whole would have been obvious under 35 U.S.C. 103, we must first delineate the invention as a whole. In delineating the invention as a whole, we look not only to the subject matter which is literally recited in the claim in question... but also to those properties of the subject matter which are inherent in the subject matter *and* are disclosed in the specification. . . Just as we look to a chemical and its properties when we examine the obviousness of a composition of matter claim, it is this invention *as a whole*, and not some part of it, which must be obvious under 35 U.S.C. 103.” *In re Antonie*, 559 F.2d 618, 620, 195 USPQ 6,8 (CCPA 1977) (emphasis in original) (citations omitted) (The claimed wastewater treatment device had a tank volume to contractor area of 0.12 gal./sq. ft. The court found the invention as a whole was the ratio of 0.12 and its inherent property that the claimed devices maximized treatment capacity regardless of other variables in the devices. The prior art did not recognize that treatment capacity was a function of the tank volume to contractor ratio, and therefore the parameter optimized was not recognized in the art to be a result-effective variable.). See also *In re Papesch*, 315 F.2d 381, 391, 137 USPQ 43, 51 (CCPA 1963) (“From the standpoint of patent law, a compound and all its properties are inseparable.”).

Obviousness cannot be predicated on what is not known at the time an invention is made, even if the inherency of a certain feature is later established. *In re Rijckaert*, 9 F.2d 1531, 28 USPQ2d 1955 (Fed. Cir. 1993). See MPEP § 2112 for the requirements of rejections based on inherency.

Emphasis added. Thus, it is quite clear that, in the context of obviousness, inherency is a very, very limited doctrine. The examiner also makes reference to MPEP § 2112 (mentioned {00274186})

in the passage above), which must be examined to better understand the limited use of inherency in obviousness:

There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure *at the time of invention*, but only that the subject matter is in fact inherent in the prior art reference. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003) (rejecting the contention that inherent anticipation requires recognition by a person of ordinary skill in the art before the critical date and allowing expert testimony with respect to post-critical date clinical trials to show inherency); see also *Toro Co. v. Deere & Co.*, 355 F.3d 1313, 1320, 69 USPQ2d 1584, 1590 (Fed. Cir. 2004) (“[T]he fact that a characteristic is a necessary feature or result of a prior-art embodiment (that is itself sufficiently described and enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention.”); *Abbott Labs v. Geneva Pharms., Inc.*, 182 F.3d 1315, 1319, 51 USPQ2d 1307, 1310 (Fed. Cir. 1999) (“If a product that is offered for sale inherently possesses each of the limitations of the claims, then the invention is on sale, whether or not the parties to the transaction recognize that the product possesses the claimed characteristics.”); *Atlas Powder Co. v. Ireco, Inc.*, 190 F.3d 1342, 1348-49 (Fed. Cir. 1999) (“Because ‘sufficient aeration’ was inherent in the prior art, it is irrelevant that the prior art did not recognize the key aspect of [the] invention.... An inherent structure, composition, or function is not necessarily known.”); *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1343-44, 74 USPQ2d 1398, 1406-07 (Fed. Cir. 2005) (holding that a prior art patent to an anhydrous form of a compound “inherently” anticipated the claimed hemihydrate form of the compound because practicing the process in the prior art to manufacture the anhydrous compound “inherently results in at least trace amounts of” the claimed hemihydrate even if the prior art did not discuss or recognize the hemihydrate)

Where applicant claims a composition in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim but the function is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 U.S.C. 102 and 103, expressed as a 102/103 rejection. “There is nothing inconsistent in concurrent rejections for obviousness under 35 U.S.C. 103 and for anticipation under 35 U.S.C. 102.” *In re Best*, 562 F.2d 1252, 1255 n.4, 195 USPQ 430, 433 n.4 (CCPA 1977). This same rationale should also apply to product, apparatus, and process claims claimed in terms of function, property or characteristic. Therefore, a 35 U.S.C. 102/103 rejection is appropriate for these types of claims as well as for composition claims

Products of identical chemical composition can not have mutually exclusive properties.” A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990) (Applicant argued that the claimed composition was a pressure sensitive adhesive containing a tacky polymer while the product of the reference was hard and abrasion resistant. “The Board correctly found that the virtual identity of monomers and procedures sufficed to support a *prima facie* case of unpatentability of Spada’s polymer latexes for lack of novelty.”)

From all of the foregoing, it is evident that inherency is a doctrine that primarily focuses on *anticipation*, usually where a composition in the prior art appears to be *the same* as that being claimed, and *must therefore exhibit the same properties or activities as the prior art*, even though that property or activity was unrecognized. However, as stated in *In re Rijckaert*, it is quite illogical to rely on inherency in the context of obviousness, which requires an analysis of what those of ordinary skill in the art *would have known at the time the invention was made*. Where the reference is silent on a feature, how could the skilled artisan be presumed to be imbued with such knowledge?

In stark contrast to the focus on anticipation and compositions of matter, there is only a passing mention of obviousness and methods in these sections of the MPEP. *Yet the issue presented here is precisely that – the obviousness of a method*. If this rejection is to be sustained, applicants submit that some case law citation is required supporting a rejection that on inherent obviousness of a method, based on the combination of two references, when it is admitted by all parties that no one has ever practiced that method in the past. Without such a citation, there simply can be no reason to sustain this rejection.

Significantly, the Federal Circuit has just issued further guidance on the notion of applying inherency in the context of obviousness in *Par Pharm. Inc. v. Alkermes Pharma Ireland Ltd.*, Case No. 2014-1391 (Fed. Cir. 2014). Not surprisingly, the court cited *In re Rijckaert*, discussed above, in arriving at the conclusion that an “inherent obviousness” rejection, while possibly proper, is highly constrained and “must be carefully circumscribed in the context of obviousness.” Indeed, this is not the sort of case where the “[m]ere recitation of a newly discovered function or property, inherently possessed by *things in the prior art, does not distinguish a claim drawn to those things from the prior art*,” citing *In re Oelrich*, 666 F.2d 578, 581 (CCPA 1981) (emphasis added). Clearly the claimed methods do not constitute part of the prior art, or the rejection would be under §102 and not §103. As such, the

fundamental principle that “obviousness cannot be predicated on what is unknown” controls here.

C. Conclusion

To conclude, the examiner has failed to establish that the general teachings of the cited art would lead the skilled artisan to the pending claims, and do so with a reasonable expectation of success. Applicants therefore respectfully request reconsideration and withdrawal of this rejection.

III. Rejections for Obviousness-Type Double-Patenting

A. Plachetka and Hassan-Alin

Claims 19, 29, 33, 34, 30, 42, and 45 have been rejected as being obvious over claims 1-55 of Plachetka in view of Hassan-Alin, both cited above. Applicants traverse.

In essence, this rejection is the same as the one immediately above, except that Plachetka is used here as the primary reference, and only the claims of Plachetka are available for citation against the present claims. Therefore, the arguments advanced above apply to Plachetka in view of Hassan-Alin with equal, and perhaps greater force, given the limited scope of citable disclosure from Plachetka. Applicants therefore respectfully request reconsideration and withdrawal of this rejection.

B. U.S. Serial No. 14/045,156

Claims 19, 29, 33, 34, 30, 42, and 45 have been provisionally rejected as being obvious over claims 57-75 of U.S. Serial no. 14/045,156. Applicants traverse.

Once again, this rejection is effectively based on the same logic as above, except that here, there is no secondary reference to rely upon, and only the claims of the ‘156 application are available for citation against the present claims. Therefore, the arguments advanced above apply here with equal, and perhaps greater force, given the limited scope of citable material

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from the '156 application. Applicants therefore respectfully request reconsideration and withdrawal of this rejection as well. Applicants therefore respectfully request reconsideration and withdrawal of this rejection.

C. U.S. Serial No. 12/822,612

Claims 19, 29, 33, 34, 30, 42, and 45 have been provisionally rejected as being obvious over claims 1-4, 18-20, 25, 26, 31, 38, 46-48, 64 and 65 of U.S. Serial no. 12/822,612.

Applicants traverse, but given that the rejection is provisional in nature, request that the rejection be held in abeyance until one of the applications at issue has matured into an issued patent.

IV. Conclusion

In light of the foregoing, applicants respectfully submit that all claims are in condition for allowance, and an early notification to that effect is earnestly solicited. The examiner is invited to contact the undersigned with any questions or comments regarding this response.

Respectfully submitted,

/Steven L. Highlander/

Steven L. Highlander
Reg. No. 37,642
Attorney for Applicants

Parker Highlander PLLC
1120 S. Capital of Texas Highway
Building One, Suite 200
Austin, Texas 78746
512-334-2900 (Telephone)
512-334-2999 (Fax)

Date: September 25, 2015

APPENDIX

Lack of Pharmacokinetic Interaction between Esomeprazole and the Nonsteroidal Anti-Inflammatory Drugs Naproxen and Rofecoxib in Healthy Subjects

M. Hassan-Alin,¹ J. Naesdal,¹ C. Nilsson-Pieschl,¹ G. Långström¹ and T. Andersson²

1 AstraZeneca R&D Mölndal, Mölndal, Sweden

2 AstraZeneca LP, Wilmington, Delaware, USA

Abstract

Background: We investigated the potential interactions between esomeprazole and a non-selective nonsteroidal anti-inflammatory drug (NSAID; naproxen) or a cyclo-oxygenase (COX)-2-selective NSAID (rofecoxib) in healthy subjects.

Methods: Two studies of identical randomised, open, three-way crossover design were conducted. Subjects ($n = 32$ for both studies) were to receive 1 week's treatment with esomeprazole 40mg once daily (studies A and B), naproxen 250mg twice daily (study A), rofecoxib 12.5mg once daily (study B), and esomeprazole in combination with naproxen (study A) or rofecoxib (study B). Study periods were separated by a 2-week washout period.

Results: On day 7 of dosing, the ratios (and 95% CIs) for the area under the plasma concentration-time curve during the dosing interval (AUC_T) and observed maximum plasma concentration (C_{max}) of esomeprazole and NSAID combination/NSAID alone were 0.98 (0.94, 1.01) and 1.00 (0.97, 1.04), respectively, for study A, and 1.15 (1.06, 1.24) and 1.14 (1.02, 1.28), respectively, for study B. The ratios (and 95% CIs) for AUC_T and C_{max} of esomeprazole and NSAID combination/esomeprazole alone were 0.96 (0.89, 1.03) and 0.92 (0.85, 1.00), respectively, for study A, and 1.05 (0.96, 1.15) and 1.05 (0.94, 1.18), respectively, for study B. All treatments were well tolerated during the study period.

Conclusion: Naproxen and rofecoxib do not interact with esomeprazole, and esomeprazole does not affect the pharmacokinetics of naproxen or rofecoxib. These findings indicate that esomeprazole can be used in combination with NSAIDs without the risk of a pharmacokinetic interaction.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used for the treatment of rheumatoid arthritis (RA), osteoarthritis (OA) and a wide variety of other acute and chronic painful musculoskeletal disorders, and can, in most countries, be used as standard analgesics and bought without a prescription. There were over 111 million NSAID prescriptions in the US for the year ending August 2000, with one-third of the total number of prescriptions being for cyclo-oxygenase (COX)-2-selective NSAIDs.^[1] The use of NSAIDs is expected to increase further in the future, especially if they become more widely used for the prevention of colorectal cancer and Alzheimer's disease. The use of low-dose aspirin for cardiovascular protection is also expected to increase.

All NSAIDs are, however, associated with a substantial number of adverse events, with non-selective NSAIDs accounting for 20% and 25% of all reported adverse drug events in the UK and US, respectively.^[2,3] NSAID-associated upper gastrointestinal (GI) tract adverse effects range from dyspeptic symptoms to peptic ulceration and ulcer complications.^[4] Some 15–40% of NSAID users report upper GI symptoms^[5] and 10–30% of long-term NSAID users will develop a peptic ulcer, predominantly in the stomach.^[6,7] NSAID use increases the risk of peptic ulcer complications by 3- to 5-fold, and 15–35% of all peptic ulcer complications are reported to be caused by NSAID use.^[4]

It has been estimated that there are over 100 000 hospital admissions per year and 16 500 deaths per year due to NSAID-induced GI complications in the US.^[8]

The anti-inflammatory properties of NSAIDs are mediated through the inhibition of the COX-2 enzyme, whereas GI adverse effects occur as a result of their action on COX-1. COX-2-selective NSAIDs, such as celecoxib and rofecoxib, preferentially inhibit COX-2. One conclusion of the VIGOR (Vioxx GI Outcomes Research) study, which com-

pared naproxen with rofecoxib in patients with RA, was that treatment with rofecoxib was associated with significantly fewer upper GI events than treatment with naproxen.^[9] Celecoxib was compared with ibuprofen and diclofenac in a similar study. The annual rates of upper GI complications were lower for celecoxib compared with ibuprofen and diclofenac, but the difference did not reach statistical significance, and the combination of celecoxib and low-dose (≤ 325 mg/day) aspirin negated the GI advantage of celecoxib.^[10] It is also worth noting that in this trial, the doses of celecoxib used were 2–4 times the maximum recommended doses for the treatment of RA and OA.

Unfavourable cardiovascular risk data has led to an urgent re-evaluation of the use of the COX-2-selective class of NSAIDs in clinical practice, culminating in the market suspension of the COX-2-selective agents rofecoxib and valdecoxib.^[11,12] The US FDA has requested that manufacturers of all marketed prescription NSAIDs revise product labeling to include a boxed warning highlighting the potential for increased risk of cardiovascular events, and is encouraging physicians to limit the use of COX-2-selective agents to the lowest practical dose for the most urgent cases.^[13] All COX-2-selective agents available in Europe contain cardiovascular warnings, and prescribers are advised to carefully regard the warnings in patients with a history of cardiovascular disease.^[14] Celecoxib is still available in the US, and celecoxib and various other COX-2-selective agents are still available in Europe.^[13,14] Additionally, during the first quarter of 2005, an FDA advisory panel recommended that rofecoxib should again be made available to patients, and that black-box warnings be placed on the labels of all COX-2-selective agents.^[15,16] Canadian health authorities may also be moving towards approving the return of rofecoxib to the market.^[17] Consequently, it does seem likely that, in the future, a range of COX-2-selective

agents may still have a role to play in the effective management of certain patients with low cardiovascular risk.

The proton pump inhibitor (PPI) omeprazole has been shown to be superior to ranitidine and misoprostol for both the healing and the prevention of NSAID-associated ulcers and dyspeptic symptoms during continued NSAID treatment.^[18,19] The degree of gastric damage caused by NSAIDs is highly dependent on intragastric pH.^[18,20] Esomeprazole, which confers a longer time with intragastric pH >4 than all other PPIs,^[21] is expected to be effective for the prevention of NSAID-associated ulcers.

As esomeprazole is expected to be widely used in the healing and prevention of gastric and duodenal ulcers, and to control upper GI symptoms in patients needing continuous NSAID treatment to relieve inflammation and pain, it is important to rule out any drug-drug interactions between esomeprazole and NSAIDs, including non-selective and selective agents. In order to test for pharmacokinetic interactions between esomeprazole and naproxen, a popular non-selective NSAID, and between esomeprazole and rofecoxib, a previously popular COX-2-selective NSAID that may still be a beneficial drug in carefully selected patients, we conducted two identically designed studies in healthy subjects.

Materials and Methods

Subjects

Healthy subjects were included if they: were 20–50 years old; had a body mass index of 19–27 kg/m²; weighed 50–95 kg; showed normal physical findings and laboratory values; had not used esomeprazole for the previous 8 weeks, any prescribed medication for the previous 2 weeks, or over-the-counter drugs (including herbal remedies, vitamins and minerals) in the week preceding the first dose of study drug; were not using anabolic

steroids; were not of childbearing potential or lactating; had no history of cardiac, renal, hepatic, neurological or significant gastrointestinal diseases; had not donated blood in the 12 weeks prior to the first dose of study drug or during the study; did not smoke or consume any other sort of nicotine (or equivalent); and were not using concomitant medications (except nasal spray for nasal congestion, or paracetamol).

The studies (study codes: SH-Nen-0016 and SH-Nen-0017) were conducted in accordance with the Declaration of Helsinki and were approved by the ethics committee of the University of Uppsala and by the Swedish Medical Products Agency. Written informed consent was received from all subjects prior to participation. The studies were performed at Quintiles AB, Uppsala, Sweden.

All subjects underwent a full clinical examination, physical examination and electrocardiogram (ECG) at pre-entry. A laboratory screen for haematology and serum biochemistry was performed prior to enrolment, on day 7 of each treatment period, and 5–7 days after the last study day.

Study Design

The two studies were conducted according to a randomised, open, three-way crossover design. Each of the three treatment periods lasted for 7 days, which was sufficient to achieve steady state. The subjects received either oral doses of an esomeprazole 40 mg capsule once daily (studies A and B), a naproxen 250 mg tablet twice daily (study A), a rofecoxib 12.5 mg tablet once daily (study B), or esomeprazole in combination with naproxen (study A) or rofecoxib (study B). Each treatment period was separated by a washout period of at least 14 days. Blood samples for determination of esomeprazole, naproxen and rofecoxib were taken for 24 hours post-dose on the last day of each treatment period. Alcohol was not allowed from 2 days before pre-entry, during each treatment period, and be-

tween the last study day and the follow-up visit. Drugs available on prescription were not allowed during the last 2 weeks preceding the studies and during the studies.

On the investigational days, the subjects arrived at the study centre in the morning, having fasted since the previous evening, for administration of the study drug and collection of repeated blood samples. On these days, standardised meals were served 4 (lunch), 6 (light meal), 10 (dinner) and 13 (light meal) hours after drug administration.

Study Drugs

In study A, the subjects received an esomeprazole 40mg capsule (Nexium®, AstraZeneca Tablet Production, Sweden)¹ once daily, a naproxen 250mg tablet (Naprosyn®, Roche, Switzerland) twice daily, or a combination of the two drugs orally for 7 days. In study B, the subjects received an esomeprazole capsule (Nexium®) once daily, a rofecoxib 12.5mg tablet (Vioxx®, MSD, Germany) once daily, or a combination of the two drugs orally for 7 days.

Blood Sampling and Bioanalytical Methods

Blood samples for assay of esomeprazole, naproxen and rofecoxib were taken at pre-dose and at 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 10, 12, 20 and 24 hours following drug administration on day 7. The blood samples were drawn from an indwelling cannula in a forearm vein and collected in heparinised tubes, centrifuged and the plasma transferred, frozen and stored until analysis.

The plasma concentration of esomeprazole was analysed using normal phase liquid chromatography with ultraviolet detection.^[22] The limit of quantification (LOQ) for this method is 25 nmol/L with a coefficient of variation (CV) of <20%. The plasma

concentration of naproxen was determined using liquid chromatography and fluorescence detection. The flow rate was 0.5 mL/min and the injection volume was 20–40 µL. The retention time was 3.0 minutes and absolute recovery in the concentration range of 0.5–500 µmol/L was between 89% and 100%. The LOQ was 0.5 µmol/L (CV ≤20%). Intra- and interassay repeatability were 4–5% and 4–6%, respectively. Rofecoxib plasma concentration was also determined using liquid chromatography and fluorescence detection. The flow rate was 1.2 mL/min and the injection volume was 150 µL. The retention time was 4.5 minutes and the absolute recovery in the concentration range of 3.0–200 nmol/L was between 90% and 91%. The LOQ was 1.5 nmol/L (CV ≤20%). Both intra- and interassay repeatability were 6–7%. The plasma samples were analysed for esomeprazole, naproxen and rofecoxib at Quintiles AB, Uppsala, Sweden.

Pharmacokinetic and Statistical Analyses

Pharmacokinetic parameters of esomeprazole, naproxen and rofecoxib were estimated by non-compartmental analysis using WinNonlin computer software. The area under the plasma concentration versus time curve during the dosing interval (AUC_T) was calculated according to a log-linear trapezoidal method. For naproxen, the AUC_T was calculated up to 12 hours post-dose, while for esomeprazole and rofecoxib the AUC_T was calculated up to 24 hours post-dose. The elimination rate constant (λ) was determined by log-linear regression analysis of the terminal slope of at least the last three plasma concentration versus time points. The terminal plasma elimination half-life ($t_{1/2}$) was calculated as $\ln 2/\lambda$. The observed maximum plasma concentration (C_{max}) and the time to reach C_{max} (t_{max}) were also recorded.

1 The use of trade names is for product identification purposes only and does not imply endorsement.

The pharmacokinetic parameters were analysed using a mixed-model analysis of variance (ANOVA) with fixed effects for sequence, period and treatment (the drug alone or in combination) and a random effect for subjects within sequences. The pharmacokinetic parameters were log-transformed prior to the analysis. Estimates and 95% confidence limits of the log-transformed parameters were anti-logarithmised, and the results are presented as geometric means and ratios with 95% confidence intervals (CIs). The median was presented for t_{\max} .

Results

Thirty-two healthy subjects (13 males and 19 females) with a mean age of 24 years and a mean bodyweight of 69kg participated in the esomeprazole and naproxen study (study A). Thirty-one subjects completed the treatment comparison of esomeprazole alone and in combination with naproxen, while 30 subjects completed the treatment comparison of naproxen alone and in combination with esomeprazole.

Thirty-two healthy subjects (15 males and 17 females) with a mean age of 26 years and a mean weight of 69kg participated in the esomeprazole and rofecoxib study (study B). Twenty-eight subjects completed the treatment comparison of esomeprazole alone and in combination with rofecoxib,

while 30 subjects completed the treatment comparison of rofecoxib alone and in combination with esomeprazole.

All those who withdrew before the end of the study did so for personal reasons. There were no safety issues.

Esomeprazole and Naproxen

Median t_{\max} values following administration of esomeprazole, naproxen and the combination are presented in table I. Estimates of the pharmacokinetic parameters with 95% CIs for esomeprazole and naproxen and the ratios with 95% CIs of the parameters are presented in table II and table III, respectively. The mean plasma concentration-time curves are shown in figure 1 and figure 2.

Both esomeprazole and naproxen were rapidly absorbed, and the median t_{\max} was approximately 1.5 hours for both drugs, both during monotherapy and during combination therapy (table I and figures 1 and 2). No changes were observed in AUC_{τ} , C_{\max} and $t_{1/2}$ for esomeprazole after co-administration with naproxen compared with esomeprazole monotherapy (see table II). The ratios (combination/esomeprazole alone) for AUC_{τ} , C_{\max} and $t_{1/2}$ were 0.96, 0.92 and 1.02, respectively, as shown in table III. For naproxen, the AUC_{τ} , C_{\max} and $t_{1/2}$ after co-administration with eso-

Table I. Median time to the observed maximum plasma concentration (t_{\max}) with minimum and maximum values following monotherapy with esomeprazole 40mg once daily, naproxen 250mg twice daily, rofecoxib 12.5mg once daily and a combination of esomeprazole with naproxen or rofecoxib for 7 days in healthy male and female subjects

Treatment	Median (h)	Minimum (h)	Maximum (h)
Study A			
Esomeprazole alone (n = 31)	1.50	1.00	2.75
Naproxen alone (n = 31)	1.50	0.75	4.00
Esomeprazole with naproxen (n = 31)	1.75	1.00	4.00
Naproxen with esomeprazole (n = 30)	1.50	0.50	4.50
Study B			
Esomeprazole alone (n = 28)	1.50	1.00	3.50
Rofecoxib alone (n = 30)	2.88	1.75	4.50
Esomeprazole with rofecoxib (n = 28)	1.50	0.75	3.50
Rofecoxib with esomeprazole (n = 30)	3.00	1.25	4.50

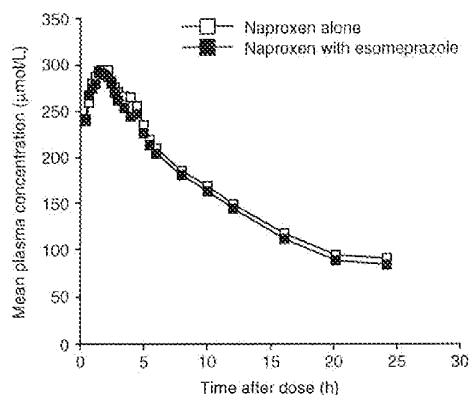


Fig. 2. Mean plasma concentration of naproxen following repeated oral administration of a naproxen 250mg tablet twice daily alone and in combination with an esomeprazole 40mg capsule once daily for 7 days in healthy male and female subjects ($n = 30$).

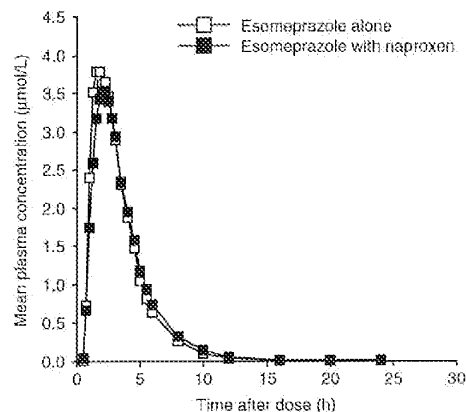


Fig. 1. Mean plasma concentration of esomeprazole following repeated oral administration of an esomeprazole 40mg capsule once daily alone and in combination with a naproxen 250mg tablet twice daily for 7 days in healthy male and female subjects ($n = 31$).

meprazole were similar to those after treatment with naproxen alone (see table II). The ratios (combination/naproxen alone) for AUC_T , C_{max} and $t_{1/2}$ were

0.98, 1.00 and 0.96, respectively, as shown in table III.

Table II. Geometric means and 95% CIs of the area under the plasma concentration vs time curve during the dosing interval (AUC_T), the observed maximum plasma concentration (C_{max}) and the terminal plasma elimination half-life ($t_{1/2}$) of esomeprazole and naproxen following repeated oral administration of an esomeprazole 40mg capsule once daily (A), a naproxen 250mg tablet twice daily (B), or a combination of an esomeprazole 40mg capsule once daily and a naproxen 250mg tablet twice daily (C), for 7 days in healthy male and female subjects

Treatment	Geometric mean	95% CI
Esomeprazole ($n = 31$)		
AUC_T ($\mu\text{mol} \cdot \text{h/L}$)		
Esomeprazole with naproxen (C)	12.22	10.61, 14.07
Esomeprazole alone (A)	12.75	11.07, 14.69
C_{max} ($\mu\text{mol/L}$)		
Esomeprazole with naproxen (C)	4.52	4.06, 5.03
Esomeprazole alone (A)	4.90	4.40, 5.45
$t_{1/2}$ (h)		
Esomeprazole with naproxen (C)	1.39	1.29, 1.50
Esomeprazole alone (A)	1.36	1.26, 1.46
Naproxen ($n = 30$)		
AUC_T ($\mu\text{mol} \cdot \text{h/L}$)		
Naproxen with esomeprazole (C)	2530.7	2420.4, 2646.1
Naproxen alone (B)	2594.2	2481.0, 2712.5
C_{max} ($\mu\text{mol/L}$)		
Naproxen with esomeprazole (C)	327.24	313.28, 341.82
Naproxen alone (B)	326.16	312.25, 340.69
$t_{1/2}$ (h)		
Naproxen with esomeprazole (C)	12.90	12.41, 13.41
Naproxen alone (B)	13.47	12.96, 14.01

Table III. Ratios of the geometric means and 95% CIs of the area under the plasma concentration vs time curve during the dosing interval (AUC_t), the observed maximum plasma concentration (C_{max}) and the terminal plasma elimination half-life ($t_{1/2}$) of esomeprazole and naproxen. Values relate to a combination of an esomeprazole 40mg capsule once daily and a naproxen 250mg tablet twice daily, divided by those following administration of an esomeprazole 40mg capsule once daily ($n = 31$) or a naproxen 250mg tablet twice daily ($n = 30$) for 7 days in healthy male and female subjects.

Treatment	Estimate	95% CI
Esomeprazole ($n = 31$)		
AUC_t (C/A)	0.96	0.89, 1.03
C_{max} (C/A)	0.92	0.85, 1.00
$t_{1/2}$ (C/A)	1.02	0.98, 1.07
Naproxen ($n = 30$)		
AUC_t (C/B)	0.98	0.94, 1.01
C_{max} (C/B)	1.00	0.97, 1.04
$t_{1/2}$ (C/B)	0.96	0.93, 0.99

A = esomeprazole, B = naproxen; C = esomeprazole/naproxen combination.

Esomeprazole and Rofecoxib

Median t_{max} values following esomeprazole, rofecoxib and the combination are presented in table I. Estimates of the pharmacokinetic parameters with 95% CIs for esomeprazole and rofecoxib are presented in table IV. The ratios of the pharmacokinetic parameters with 95% CIs are presented in table V. The mean plasma concentration-time curves are shown in figure 3 and figure 4.

Esomeprazole was rapidly absorbed with a t_{max} of 1.5 hours, while the median t_{max} for rofecoxib was approximately 3 hours, both with rofecoxib alone and in combination with esomeprazole (table I). The AUC_t , C_{max} and $t_{1/2}$ for esomeprazole were not affected by rofecoxib (table IV). The ratios (combination/esomeprazole alone) for AUC_t , C_{max} and $t_{1/2}$ were 1.05, 1.05 and 0.99, respectively, as shown in table V. For rofecoxib, there was a slight increase in AUC_t and C_{max} after co-administration with esomeprazole compared with rofecoxib monotherapy (table IV). The ratios (combination/rofecoxib alone) for AUC_t , C_{max} and $t_{1/2}$ were 1.15, 1.14 and 1.06, respectively, as shown in table V.

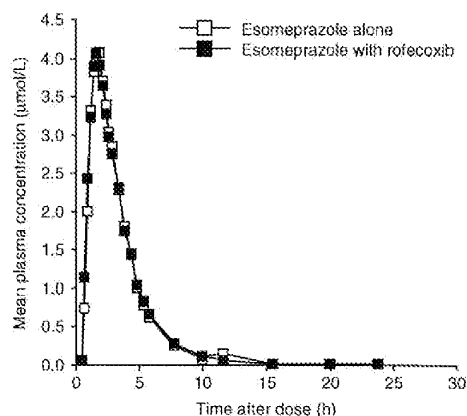


Fig. 3. Mean plasma concentration of esomeprazole following repeated oral administration of an esomeprazole 40mg capsule once daily alone and in combination with a rofecoxib 12.5mg tablet once daily for 7 days in healthy male and female subjects ($n = 28$).

Discussion

Esomeprazole is expected to be widely used in the management of upper GI symptoms, and to heal and prevent gastric and duodenal ulcers associated with continued NSAID use. Therefore, esomeprazole will commonly be used in combination with NSAIDs. Although it seems likely that in most

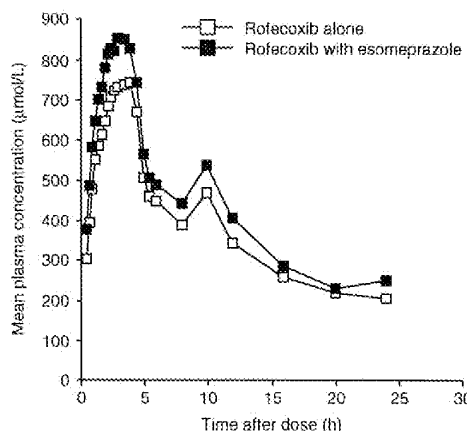


Fig. 4. Mean plasma concentration of rofecoxib following repeated oral administration of a rofecoxib 12.5mg tablet once daily alone and in combination with an esomeprazole 40mg capsule once daily for 7 days in healthy male and female subjects ($n = 30$).

Table IV. Geometric means and 95% CIs of the area under the plasma concentration vs time curve during the dosing interval (AUC_{τ}), the observed maximum plasma concentration (C_{max}) and the terminal plasma elimination half-life ($t_{1/2}$) of esomeprazole and rofecoxib following repeated oral administration of an esomeprazole 40mg capsule once daily (A), a rofecoxib 12.5mg tablet once daily (B), or a combination of an esomeprazole 40mg capsule once daily and a rofecoxib 12.5mg tablet once daily (C) for 7 days in healthy male and female subjects

Treatment	Geometric mean	95% CI
Esomeprazole (n = 28)		
<i>AUC_τ (μmol • h/L)</i>		
Esomeprazole with rofecoxib (C)	12.57	10.47, 15.10
Esomeprazole alone (A)	11.99	9.98, 14.40
<i>C_{max} (μmol/L)</i>		
Esomeprazole with rofecoxib (C)	4.88	4.18, 5.70
Esomeprazole alone (A)	4.63	3.96, 5.41
<i>t_{1/2} (h)</i>		
Esomeprazole with rofecoxib (C)	1.39	1.25, 1.56
Esomeprazole alone (A)	1.41	1.26, 1.57
Rofecoxib (n = 30)		
<i>AUC_τ (μmol • h/L)</i>		
Rofecoxib with esomeprazole (C)	9.61	8.37, 11.04
Rofecoxib alone (B)	8.36	7.28, 9.61
<i>C_{max} (μmol/L)</i>		
Rofecoxib with esomeprazole (C)	0.89	0.78, 1.01
Rofecoxib alone (B)	0.78	0.68, 0.88
<i>t_{1/2} (h)</i>		
Rofecoxib with esomeprazole (C)	12.91	11.58, 14.40
Rofecoxib alone (B)	12.17	10.91, 13.58

cases the NSAID in question will be a non-selective agent, use of COX-2-selective agents has not been ruled out, and certain patients may still benefit from

these agents. The aim of the present study was to rule out any potential for drug-drug interaction between esomeprazole and naproxen, being a representative non-selective NSAID, and rofecoxib, as an example of a COX-2-selective NSAID.

Esomeprazole plasma levels were not affected by naproxen or rofecoxib. The AUC_{τ} , C_{max} and $t_{1/2}$ for esomeprazole after co-administration with naproxen or rofecoxib were similar to those after esomeprazole alone. The AUC_{τ} , C_{max} and $t_{1/2}$ of naproxen after co-administration with esomeprazole were similar to those after naproxen alone. There was a marginal increase in AUC_{τ} and C_{max} for rofecoxib during the combination therapy compared with rofecoxib administered alone. The slight pharmacokinetic changes seen would not be expected to have any clinical relevance. Rofecoxib has double plasma concentration-time profiles when administered alone⁽²³⁾ and in combination with esomeprazole (figure 4). This may be due to redistri-

Table V. Ratios of the geometric means and 95% CIs of the area under the plasma concentration vs time curve during the dosing interval (AUC_{τ}), the observed maximum plasma concentration (C_{max}) and the terminal plasma elimination half-life ($t_{1/2}$). Values relate to a combination of an esomeprazole 40mg capsule once daily and a rofecoxib 12.5mg tablet once daily, divided by those following administration of an esomeprazole 40mg capsule once daily (n = 28) or a rofecoxib 12.5mg tablet once daily (n = 30) in healthy male and female subjects

Treatment	Estimate	95% CI
Esomeprazole (n = 28)		
AUC_{τ} (C/A)	1.05	0.96, 1.15
C_{max} (C/A)	1.05	0.94, 1.18
$t_{1/2}$ (C/A)	0.99	0.90, 1.08
Rofecoxib (n = 30)		
AUC_{τ} (C/B)	1.15	1.06, 1.24
C_{max} (C/B)	1.14	1.02, 1.28
$t_{1/2}$ (C/B)	1.06	0.97, 1.16

A = esomeprazole; B = rofecoxib; C = esomeprazole/rofecoxib combination.

bution or to an enterohepatic circulation phenomenon. We do not know the reason(s) for the double profile for rofecoxib; however, this is a normal concentration-time profile for rofecoxib.^[23]

Pharmacokinetics is one of the factors that may influence the NSAID safety profile. Although the majority of marketed NSAIDs are well absorbed, metabolised extensively, subject to fairly minimal first-pass extraction, and have linear pharmacokinetics, some more subtle differences are apparent.^[24] Esomeprazole metabolism is mediated by cytochrome P450 (CYP) isoforms, CYP2C19 and CYP3A4,^[25] while the NSAIDs have been shown to be mainly metabolised by another CYP isoform, CYP2C9.^[26] On the basis of this knowledge, a drug interaction would not be expected between esomeprazole and the NSAIDs. However, a recently published study has reported that the extent of the role of CYP2C9 in the overall clearance of different NSAIDs is varied, and that CYP3A4 activity can sometimes be involved.^[24] We feel that a lack of drug interactions during combination therapy with esomeprazole and all available NSAIDs should not be assumed, but rather evaluated on an individual basis. The results of the present interaction study help to confirm that drug-drug interactions are not an issue between esomeprazole and naproxen or rofecoxib. This study is also in agreement with previous studies involving omeprazole, which showed no drug-drug interactions between omeprazole and three different NSAIDs (naproxen, diclofenac or piroxicam).^[27]

Conclusion

Neither naproxen nor rofecoxib have any effect on the pharmacokinetics of esomeprazole, and esomeprazole does not have any effect on the pharmacokinetics of naproxen or rofecoxib. The clinical implications of these findings are that esomeprazole can be used together with naproxen or rofecoxib without pharmacokinetic drug interaction

safety concerns for the healing and prevention of gastric and duodenal ulcers in patients needing continuous NSAID treatment to relieve inflammation and pain. Repeated oral administration of esomeprazole alone, as well as in combination with naproxen or rofecoxib, was well tolerated.

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Correspondence and offprints: Dr M. Hassan-Alin, Clinical Pharmacology, AstraZeneca R&D Mölndal, S-431 83 Mölndal, Sweden.
E-mail: mohammed.hassan-alin@astrazeneca.com