



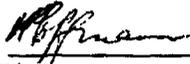
1103326-0072CIP

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Inventor Application of : Lindberg, et al.  
 Serial No. : 08/376,512  
 Filed : January 23, 1995  
 For : NEW COMPOUNDS  
 Examiner : J. FAN  
 Group Art Unit : 1203

#11  
3/14/97

I hereby certify that this paper is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks Washington, D.C. 20231.

Hans-Peter G. Hoffmann 37,352  
 Attorney Name PTO Reg. No.  
 2/12/97  
 Signature Date of Signature

Assistant Commissioner for Patents  
Washington, D.C. 20231

**DECLARATION OF ANDERSSON**  
(Under 37 C.F.R. § 1.132)

Sir:

I, Tommy Andersson Ph.D., declare as follows: I am a citizen of SWEDEN. I graduated in 1991 from the University of Gothenburg with a doctorate in Clinical Pharmacology.

I have been employed from 1978 to the present by Astra Hässle AB which company is owned by Astra Aktiebolag,

0000EL8P.W51

the assignee of the referenced application. I have read and understood the referenced patent application and I am familiar with the invention described and claimed therein. My curriculum vitae is enclosed (Exhibit A).

Set forth below is a summary of two clinical studies, Study A and Study B, performed by Astra Hässle AB on the pharmaceutical formulations of omeprazole and its enantiomers having the chemical name, 5-methoxy-2-(((4-methoxy-3,5-dimethyl-2-pyridinyl)methyl) sulfinyl)-1H-benzimidazole. As used herein, omeprazole refers to the racemate of its (+) and (-) enantiomers, and its (+) and (-) enantiomers are designated (+)-omeprazole and (-)-omeprazole, respectively.

Study A concerns a clinical comparison of the pharmacokinetics of the sodium salts of (-)-omeprazole and of (+)-omeprazole with the sodium salt of omeprazole racemate and an assessment of the interindividual difference or variation in relative bioavailability when administered perorally to "slow" and "rapid" metabolizers.

Study B involves peroral treatment of patients suffering from gastroesophageal reflux disease with the magnesium salt of (-)-omeprazole and racemic omeprazole non-salt form and a comparison of the inhibitory effect on gastric acid secretion measured as the duration of elevated

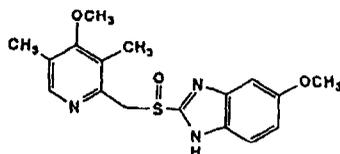
intra-gastric pH. Study B also involves the assessment of interindividual variation in plasma concentrations.

My conclusion based on these clinical studies is that the (-)- enantiomer omeprazole, unexpectedly has a different and more advantageous pharmacokinetic profile in terms of interindividual variation than both the (+)-enantiomer of omeprazole and the omeprazole racemate. This is contrary to the prior art teaching on the pharmacodynamic effect which was previously demonstrated in gastric glands to be the same for the two enantiomers as would be expected, (see Erlandsson, et al., Journal of Chromatography, 532 (1990) 305-319 p. 318), since the drug's mechanism of action involves a non-chiral active inhibitor formed in the compartments of the parietal cell with the same rate of reaction from both enantiomers. The non-chirality of the active form of omeprazole is an uncommon occurrence among chiral drugs where the activity usually resides in only one of the two enantiomers, the other being substantially less active.

#### **Chemical Background**

Omeprazole is a racemic mixture (racemate), containing the two enantiomers, the (+)-enantiomer of omeprazole and the (-)-enantiomer of omeprazole. This is

due to the chirality of the sulfoxide moiety in the omeprazole molecule of the following formula



The (-)-enantiomer of omeprazole and the (+)-enantiomer of omeprazole are simply designated (-)-omeprazole and (+)-omeprazole, respectively.

As described in the referenced patent application, U.S. Serial No. 08/376,512, the alkaline salts of each of the single enantiomeric forms of omeprazole were obtained in solid state form which made it possible to further purify the salts by recrystallization attaining both high chemical and optical purity. In contrast, the neutral form of the (-)-enantiomer of omeprazole has only been obtained in the prior art in oil form. The oil form is difficult to formulate into stable reproducibly defined dosage forms, a problem which was overcome by the use of the alkaline salt forms of the enantiomers.

#### Biological Background

Omeprazole which is formulated into an enteric coated formulation and marketed in the U.S.A. as Prilosec®

is a proton pump ( $H^+/K^+$ -ATPase) inhibitor which has been used for several years in the treatment of gastric acid-related diseases with good clinical results. A safety assessment, based on more than 200 million prescriptions worldwide, indicates that omeprazole is a safe drug with no reports of dose-dependent side effects.

*"Slow and "Rapid" metabolizers"*

It is known that some individuals (about 3% among Caucasians and about 15% among Asians) exhibit higher (5- to 10-fold) than average plasma concentration versus time curves (AUC) of the drug. The metabolic capacity of this minority of individuals, who are classified as slow or poor metabolizers (as opposed to the majority who are classified as rapid/extensive or "normal" metabolizers), is genetically determined. Omeprazole is mainly metabolized by the polymorphically expressed enzyme CYP2C19. It has been found that the reason for slow metabolism is a lack of activity of the main omeprazole-metabolizing enzyme, the cytochrome P450 (CYP) isoform CYP2C19. Thus, while rapid metabolizers express an active CYP2C19, the slow metabolizers do not. This means that the difference in plasma levels of omeprazole between those who express an active form of this liver enzyme and those who do not is substantial. This leads to a certain degree of inter-

individual variation in plasma levels within the total population during treatment with omeprazole. Thus, there is several fold difference in plasma levels between those individuals who express a functional enzyme (rapid metabolizers) and those who do not (slow metabolizers).

**Study A: (-)-Omeprazole in healthy volunteers**

The objective of this study was to compare the pharmacokinetics of sodium salts of (-)-omeprazole; (+)-omeprazole; and racemic omeprazole following repeated oral administration of daily 60 mg doses of each compound to slow metabolizers of omeprazole and daily 15 mg doses of each compound to rapid metabolizers.

A secondary objective was to study the effect on gastric acid secretion of the different compounds in rapid metabolizers.

An open three-way, randomized, cross-over study was conducted consisting of three treatment periods, each with a duration of 7 days and each separated by a washout period of 2 weeks. The pharmacokinetics (plasma levels) of the compounds were studied in all subjects on day 1 and day 7 of each treatment period and the effect on acid secretion was studied in the rapid metabolizers on day 7 of each treatment period.

Five slow metabolizers (as assessed by the S/R mephenytoin urinary ratio) and four rapid metabolizers of omeprazole completed the study. The subjects were healthy males varying from 21 to 38 years of age.

The sodium salts of (-)-omeprazole, (+)-omeprazole and racemic omeprazole, respectively were administered in the form of an oral solution (5mg/ml). In order to neutralize the gastric acid of the subject and hence avoid degradation of the acid labile compounds, bicarbonate solution was administered with the drug solution. Further bicarbonate solution was given to the subject 5 minutes prior to and 10, 20, and 30 minutes after dose administration.

#### Summary of Results

Fig. 1 of Exhibit B shows mean plasma levels of the racemic omeprazole, the single (-)-omeprazole enantiomer and the single (+)-omeprazole enantiomer at steady state (Day 7) in rapid metabolizers following administration of 15 mg doses of the sodium salt of each compound. The mean AUC at steady state of (-)-omeprazole was almost 90% higher than that of racemic omeprazole while that of (+)-omeprazole was about one-third of that of the racemic omeprazole. Since the inhibitory effect on gastric acid secretion of omeprazole or its enantiomers is directly correlated to the AUC level irrespective of the

enantiomeric form of the compound administered, this characteristic results as shown in Study B in a more pronounced inhibitory effect on gastric acid secretion by the (-)-omeprazole compared to that of the racemic omeprazole.

Fig. 2 of Exhibit B shows the mean plasma levels of omeprazole racemate, (+)-omeprazole and (-)-omeprazole at steady state (Day 7) in slow metabolizers following administration of 60 mg doses of the sodium salts of each compound. In slow metabolizers, the mean AUC at steady state of (-)-omeprazole was about 30% lower than that of racemic omeprazole while the AUC of (+)-omeprazole was higher.

After adjusting for the different dose levels, the AUC of (-)-omeprazole was found to be about 3 fold greater in slow metabolizers than in rapid ("normal") metabolizers. With (+)-omeprazole, on the other hand, the difference in AUC between slow and rapid metabolizers was much greater (approximately 30-fold). Racemic omeprazole, being the mixture of the two enantiomers, exhibits about a 10-fold difference in AUC between slow and rapid metabolizers. Thus (-)-omeprazole gives a substantially smaller ratio in AUC between rapid and slow metabolizers compared to both (+)-omeprazole and racemic omeprazole, which demonstrates that (-)-omeprazole is less dependent on

CYP2C19 for its metabolism than is the (+)-omeprazole or the racemic omeprazole.

**Conclusions from Study A**

- The difference in AUC between slow and rapid metabolizers was only 3-fold for (-)-omeprazole, as compared to 10- and 30-fold for omeprazole racemate and (+)-omeprazole, respectively.
- In rapid metabolizers the AUC of (-)-omeprazole was approximately 2-fold higher than that of omeprazole racemate resulting in a more pronounced acid inhibitory effect.

**Study B: (-)-Omeprazole in reflux patients**

A study was conducted in 38 patients with symptomatic gastroesophageal reflux disease in which the effects on 24 hour intragastric acidity by oral treatment with 20 mg omeprazole racemate (capsules) and the magnesium salt of (-)-omeprazole (corresponding to 20 mg or 40 mg of the neutral compound) were compared. In addition, the plasma concentrations of (-)-omeprazole and omeprazole racemate were determined on the last treatment day (day 5).

The study was conducted as a double-blind, randomized, three-way cross-over trial consisting of three study periods, each with five days of daily oral administration of formulations containing the magnesium salt of (-)-omeprazole or omeprazole racemate separated by a wash-out period of at least two weeks. The 38 patients

(22 females) ranged in age from 29-58 years. 32 of the patients were *Helicobacter pylori* negative.

Enteric coated pellets comprising the magnesium salt of (-)-omeprazole were filled in hard gelatin capsules calculated to correspond to either 20 mg or 40 mg of neutral (-)-omeprazole compound.

These formulations were compared with an identical treatment except for using enteric coated pellets comprising omeprazole filled in a hard gelatin capsule containing 20 mg racemic omeprazole in the non-salt form (Prilosec®).

The intragastric pH was recorded over 24 hours on day five of each study period upon administering the fifth dose.

#### Summary of Results

The study was completed by 36 patients and the results therefrom were statistically evaluated. The effects of the treatments on intragastric pH are summarized in Table 1 and the AUC values are shown in Table 2.

As shown in Table 1 the percentage of time (of the 24-hour period assessed) with pH above 4 (a direct measure of inhibitory effect on gastric acid secretion) was 44% for 20 mg omeprazole racemate and 53% for 20 mg (-)-omeprazole ( $p < 0.0001$ ), which means that patients treated with (-)-omeprazole will have 2.2 hours longer time with pH

above 4 than those treated with omeprazole racemate in corresponding doses.

Table 1. Least square estimates and 95% confidence intervals for the true mean treatment effects, regarding percentage of time with pH>4 during 24 hours.

Treatment	Estimate	Lower	Upper
Omeprazole 20 mg	43.7	36.7	50.7
(-)ome 20 mg	53.0	46.0	60.0
(-)ome 40 mg	69.8	62.8	76.8

The data of Table 2 shown below demonstrate that the AUC of (-)omeprazole is significantly higher than that of racemic omeprazole at the 20 mg dose, and the 40 mg dose of (-)omeprazole produced a significantly higher AUC than the 20 mg dose of (-)-omeprazole ( $p < 0.0001$ ).

The interindividual variation in AUC and thus the inhibitory effect is less pronounced following administration of (-)-omeprazole than following administration of omeprazole racemate. This was judged by the coefficient of variation for the mean AUC which was 59% for 20 mg of the magnesium salt of (-)-omeprazole and 88% for 20 mg of omeprazole racemate ( $p < 0.0001$ ).

Table 2. Least square estimates and 95% confidence intervals for the true mean treatment effects, regarding AUC ( $\mu\text{mol} \times \text{h/L}$ ).

Treatment	Estimate	Lower	Upper
Omeprazole 20 mg	2.3	1.8	3.0
(-)-ome 20 mg	4.2	3.3	5.4
(-)-ome 40 mg	12.6	9.9	16.2

**Conclusions from Study B**

- Patients treated with the magnesium salt of (-)-omeprazole had a longer time with pH above 4 as a result of almost 2-fold higher AUC's obtained compared with racemic omeprazole.
- Patients treated with the magnesium salt of (-)-omeprazole exhibited less interindividual variation in AUC than observed with racemic omeprazole.

**Clinical relevance of results from Study A and B with (-)-omeprazole administered as alkaline salt.**

*A larger fraction of patients will have optimal plasma concentrations with (-)-omeprazole*

As a consequence of the less pronounced difference in AUC between slow and rapid metabolizers, the interindividual variation in AUC of (-)-omeprazole is less than that of omeprazole. Furthermore, available data indicate that the interindividual variation in AUC of (-)-omeprazole within the group of rapid metabolizers also is less than that observed for omeprazole racemate. These

02/12 13:40 1997

FROM:

+ 1 776 3790

TO: 12128192582

PAGE: 2

'97 02/12 17:14

+46 31 776 3790

PAG ASTRA HASSLE

0002

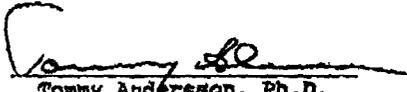
110324-0732

- less interindividual variation in plasma levels (AUC), both between rapid and slow metabolizers and within the group of rapid metabolizers, provides for a larger fraction of patients with optimal plasma concentrations with respect to desired antisecretory effect
- higher average AUC results in a more pronounced inhibitory effect on gastric-acid secretion and is expected to result in a better overall clinical effect

Thus, the alkaline salts of (-)-omeprazole can provide an improved, alternative pharmaceutical formulation for the treatment of gastric acid-related diseases.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Dated: February 12, 1997

  
Tommy Andersson, Ph.D.

000016P.W51

-14-

(TUE) 02 11 17 20:05/NO. 9561787140 P 15/28

OM WAC NY FAX DEPT

- less interindividual variation in plasma levels (AUC), both between rapid and slow metabolizers and within the group of rapid metabolizers, provides for a larger fraction of patients with optimal plasma concentrations with respect to desired antisecretory effect
- higher average AUC results in a more pronounced inhibitory effect on gastric-acid secretion and is expected to result in a better overall clinical effect

Thus, the alkaline salts of (-)-omeprazole can provide an improved, alternative pharmaceutical formulation for the treatment of gastric acid-related diseases.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Dated:

\_\_\_\_\_  
Tommy Andersson, Ph.D.

characteristics taken together may potentially result in a larger fraction of patients attaining plasma concentrations which would be optimal with respect to the desired gastric acid anti-secretory effect in the clinical situation.

*Higher AUC giving better overall clinical effect with (-)-omeprazole*

It was observed that the steady-state AUC of (-)-omeprazole in an average population was significantly higher (2-fold) than that of omeprazole racemate when each compound was given repeatedly in 20 mg daily doses. Therefore, the anti-secretory effect, which is directly correlated to the AUC irrespective of compound, was higher for (-)-omeprazole than for omeprazole racemate following administration of identical doses. This is expected to give a clinical advantage for (-)-omeprazole, since the number of patients healed from the acid-related disease is expected to be higher, and healing is also expected to be achieved within a shorter time frame. It might also be expected that a more rapid symptom relief will be obtained.

**Conclusion:**

The clinical studies outlined above demonstrate that the alkali metal salts of (-)-omeprazole, have the following unexpected pharmacokinetic advantages over the omeprazole racemate:

From: BRUCE RADIN, ESQ (973)379-4800  
BUDD LARNER GROSS ROSENBAUM  
150 JOHN F. KENNEDY PKWY  
3RD FLOOR  
SHORT HILLS, NJ, 07078

REVENUE BARCODE



To: Janet Woodcock, M.D., Director (301)594-5400  
Food and Drug Administration  
HFD-1 - Woodmont Office Complex 2  
1451 Rockville Pike  
Rockville, MD, 20857

SHIP DATE: 27AUG  
WEIGHT: 1 LBS

Ref: 001483-00065



DELIVERY ADDRESS BARCODE(FEDEX-EDK)

TRK # 7920 9550 6675 6281

FedEx PRIORITY OVERNIGHT

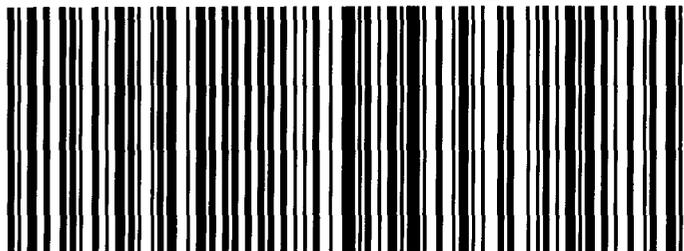
WED

A2

Deliver by:  
28AUG

20857-MD-US

IAD  
ZM GAIA



### Shipping Label

Schedule Courier

Find a Dropoff Location

Shipping History

Shipment Complete

Cancel Shipment

Edit Shipment Information

1. Use the "Print" feature from your browser to send this page to your laser printer.
2. Fold the printed page along the horizontal line.
3. Place label in air waybill pouch and affix it to your shipment so that the barcode portion of the label can be read and scanned.

### Shipment Details

To print a copy of the shipment information for your records, please click "Shipment Details".

Shipment Details

### Ship a New Package

Ship Inside U.S.

Ship Outside U.S.

Ship to Same Recipient

Use of this system constitutes your agreement to the service conditions in the current FedEx service Guide, available upon request. FedEx will not be responsible for any claim in excess of \$100 per package, whether the result of loss, damage, delay, non-delivery, misdelivery, or misinformation, unless you declare a higher value, pay an additional charge, document your actual loss and file a timely claim. Limitations found in the current FedEx Service Guide apply. Your right to recover from FedEx for any loss, including intrinsic value of the package, loss of sales, income interest, profit, attorney's fees, costs, and other forms of damage whether direct, incidental, consequential, or special is limited to the greater of \$100 or the authorized declared value. Recovery cannot exceed actual value.