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OMEPRAZOLE MUPS®: AN ADVANCED FORMULATION OFFERING FLEXIBILITY AND PREDICTABILITY FOR SELF MEDICATION

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ABSTRACT

INTRODUCTION: The MUPS®* tablet formulation of omeprazole magnesium is now in widespread use as a consumer medicine in Europe and the United States (US). On December 8th 2010 a panel of experts was assembled in Zurich to review the accumulated evidence on omeprazole MUPS® and the contribution of the pharmaceutical, pharmacokinetic and pharmacodynamic features of this formulation to clinical efficacy in the treatment of symptomatic reflux disease.

FORMULATION: The MUPS® tablet is a patented formulation of omeprazole designed to optimise delivery of omeprazole to the site of its absorption in the small intestine. In particular the gastro-resistant properties of the multiple layered micropellets are important to protect the acid-labile omeprazole from gastric juice. Many generic omeprazole formulations are now available for consumer purchase in some European markets. Dissolution studies with a variety of omeprazole formulations confirm substantial differences in speed and degree of omeprazole release under differing pH conditions designed to mimic gastric passage and duodenal delivery. Omeprazole formulations available for consumers to purchase cannot be considered interchangeable with regard to pharmaceutical properties.

PHARMACOKINETICS AND PHARMACODYNAMICS: Omeprazole is an inactive prodrug which requires nonenzymatic, proton-catalyzed conversion to an active sulphenamide intermediate in the secretory cannaliculi of the parietal cell, this then binds to and inactivates the H+K+-ATPase 'proton pump'. Omeprazole MUPS® tablets are bioequivalent to the originally marketed omeprazole capsules and produce similar pharmacodynamic effects on gastric secretion in direct comparison studies. In comparison to capsules, however, bioavailability from the MUPS® tablet is somewhat faster in the fed state. Bioavailability of omeprazole increases between day 1 and day 6 of dosing and this is reflected in an increased pharmacodynamic effect (median gastric pH) compared to pantoprazole 40mg at day 6 but an equivalent effect on day 1.

HEARTBURN STUDIES IN CONSUMERS: Heartburn is very common in the general population and 20% of sufferers have symptoms more often than weekly. Endoscopy is not warranted in these individuals unless 'alarm' symptoms (e.g. anaemia, dysphagia, weight loss) are present. In surveys, frequent sufferers want complete and long lasting relief from heartburn. Large clinical studies with the MUPS® formulation in the US confirm that high proportions of both day and night time periods are reported as free of heartburn on regular dosing for 14 days with omeprazole MUPS® 20mg and 10mg. A naturalistic study of consumer compliance with US label instructions for omeprazole MUPS® showed that self-selection for treatment

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was appropriate in the great majority of participants and very few exceeded the mandated 14 days of treatment without medical advice.

PRESCRIPTION EXPERIENCE WITH MUPS® AND GENERIC OMEPRAZOLE: In the Netherlands, a large study comparing omeprazole MUPS® 20mg, lansoprazole 30mg and pantoprazole 40mg in patients with symptomatic grade I-IV reflux oesophagitis confirmed similar high levels of patient satisfaction with all drugs after 4 and 8 weeks. The popularity of PPIs for acid related conditions in the Netherlands, as elsewhere, has led to increasing levels of usage and an associated rise in costs. Since the loss of patent protection in 2004, more than 50 generic versions of omeprazole have been launched in the Netherlands. Studies of omeprazole release characteristics from examples of these preparations show variable rates of drug delivery and some evidence that 'dose dumping' may occur and potentially affect efficacy. The absorption, distribution and activation of omeprazole in functioning proton pumps is a complex series of processes that may not be adequately represented by narrowly defined bioequivalence determined on pharmacokinetic grounds. The suggestion that generic formulations may exhibit pharmacodynamic and clinical differences compared to the originator drug, is lent some indirect support by the results of a survey of 5,254 users of generic omeprazole in the Netherlands. This found that around 20% of users required substitution of originator omeprazole or another PPI on grounds of unsatisfactory response to generic omeprazole treatment.

SUMMARY: The omeprazole MUPS® formulation is a carefully designed galenic form which optimises delivery of the drug to the site of activation and pharmacodynamic action, particularly in the fed state. The small easily swallowed tablet can also be dispersed in water. This formulation has been well characterised in pharmacokinetic, pharmacodynamic and clinical studies. In particular omeprazole MUPS® has been shown to produce substantial freedom from heartburn in a frequently suffering population during 14 days of use. When recommending a PPI for appropriate consumers, health care professionals should consider this level of evidence and be aware that not all omeprazole formulations can be considered as interchangeable in clinical use.

Key words: Omeprazole, MUPS®, Gastro-resistant formulation, Bioequivalence.

FEATURES OF THE MUPS® FORMULATION - Jérôme Aubert, Pharm D

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Omeprazole is a pro-drug that accumulates in the acid space of the parietal cell where it is transformed to the active state. However the drug has several characteristics which determine its access to this site of action. Omeprazole is a weak base which is stable at neutral pH but decomposes rapidly in an acidic environment. Therefore, in order for it to reach the small intestine where it is absorbed, it must be protected from gastric fluid when administered orally. These properties pose challenges for drug formulators seeking to provide optimal delivery of the drug.

The MUPS® tablet formulation of omeprazole employs patented technology in a delivery system which disperses rapidly in the stomach to release about 1,000 small (0.5mm) individually enteric coated units or 'micropellets' of omeprazole as the magnesium salt. These pellets are designed to dissolve in the high pH of the small intestine to release omeprazole for absorption.

The manufacture of MUPS® tablets has multiple steps. First omeprazole magnesium is micronized before suspension and layering onto sugar microspheres (0.250-0.355mm). These pellets are then sub-coated to separate the omeprazole from the enteric coating which is applied next. The pellets are then given a final protective over-coating before being mixed with tabletting excipients and compressed into tablets which themselves are film-coated.

Thus each MUPS® pellet has a 4 layer 'onion' structure and each tablet is comprised of multiple pellets which are apparent if the tablet is broken (figure 1).

FIGURE 1: PELLET STRUCTURE APPARENT IN BROKEN MUPS® TABLETS.

In vitro dissolution testing of the tablets confirms the USP specifications required to meet the key formulation characteristic of gastro-resistance. In the first or 'gastric phase', dissolution of the tablets in acid pH 1 (HCl 0.1 M) stirred for 2 hours (100 rpm paddle speed) is measured, and not less than 90% of the omeprazole content should remain intact in the pellets. Subsequently in the 'small intestine' or drug release phase, dissolution at pH 6.8 is measured and after 45 minutes not less than 75% of the stated omeprazole content should be released. Changes in the quantity of enteric coating and protective overcoating can be shown to have an effect on gastric resistance as can tablet hardness which varies with the punch force used to produce the tablets.

Since the expiry of the patent on omeprazole, numerous generic copies have been marketed. The introduction of omeprazole as a non-prescription or 'over the counter' (OTC) medicine in some countries has also led to an explosion in the availability of alternative generic versions. For example in Germany there are more than 20 'OTC' formulations of omeprazole although only a few of these are tablets (one of which is the Bayer MUPS® product) with the majority being capsule formulations.

The pharmaceutical quality and properties of these generic products may vary and analytical techniques to examine them (e.g. the dissolution testing described above) may not be very discriminative. A study of the pharmaceutical quality of 7 local omeprazole capsule brands in Egypt was assessed relative to the proprietary product (Losec®)[1]. All brands passed the USP drug release test (omeprazole release from capsules at pH 6.8 after pre-exposure to pH 1 for 2 hours) as shown in Figure 2. However a modified release test (omeprazole release profile at pH 6.8 after pre-exposure to pH 4 for 2 hours) proved to be more discriminative between formulations (see Figure 3). Pre-exposure to this latter pH may reflect more closely both the gastric pH after food and during ongoing acid suppression with omeprazole.

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FIGURE 2: RELEASE PROFILE OF DIFFERENT BRANDS OF OMEPRAZOLE CAPSULES AT PH 6.8 AFTER PRE-EXPOSURE TO PH 1 FOR 2 HOURS (Adapted from Reference 1).

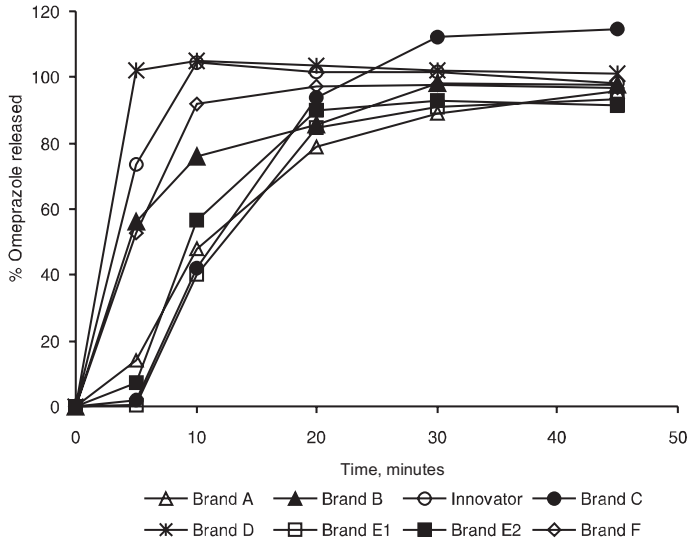
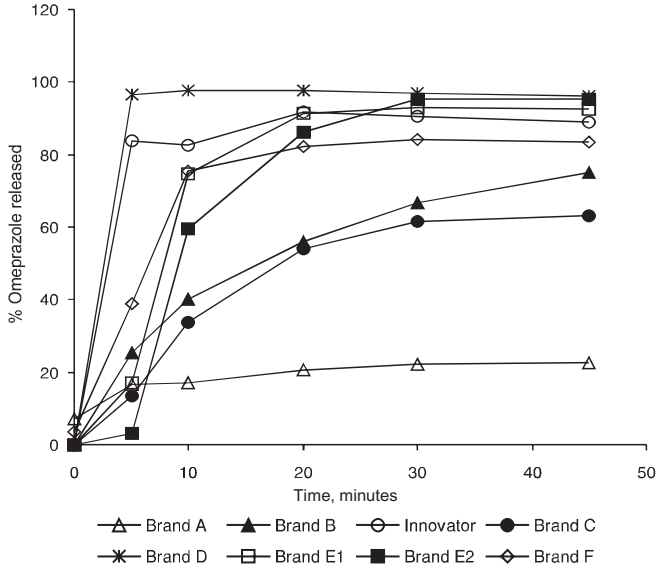


FIGURE 3: RELEASE PROFILE OF DIFFERENT BRANDS OF OMEPRAZOLE CAPSULES AT PH 6.8 AFTER PRE-EXPOSURE TO PH 4 FOR 2 HOURS (Adapted from Reference 1).



In this study and others[2,3] using a stability test performed under accelerated conditions (40 degrees Centigrade, 75% relative humidity, during a four month period) the investigators concluded that progressive darkening of the pellets from some capsule formulations was associated with very low dissolution performance.

SUMMARY

The omeprazole MUPS® tablet formulation (protected by a patent valid until 2014) is an innovative product designed to deliver the maximal amount of omeprazole to the site of absorption in the small intestine by protecting it in micropellets during passage through the stomach. Although

many other enteric formulations have been produced (most delivering enteric coated pellets via a capsule), not all of these have the same release characteristics and this in turn could produce differences in bioavailability. Omeprazole products available for consumers to purchase cannot be considered interchangeable with regard to their pharmaceutical properties.

PHARMACOKINETICS AND PHARMACODYNAMICS OF THE OMEPRAZOLE MUPS® TABLET FOR THE TREATMENT OF ACID-RELATED SYMPTOMS - Prof. Dr. med. Karsten Schrör

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PHARMACOKINETICS

Omeprazole is an inactive prodrug that needs to be converted into an active form by nonenzymatic, proton-catalyzed generation of a sulphenamide intermediate. This non-chiral metabolite binds long-lastingly to the catalytic subunit of H+K+-ATPase in the secretory membranes of the parietal cells of the gastric mucosa.

The half-life of unmetabolized omeprazole is pH-dependent: *in vitro* at pH 1 it is 1-2 minutes but at pH 7.4 this increases to about 20 hours. *In vivo*, the plasma half-life of unmetabolized omeprazole is 1-2 hours while its half-life at the site of action is 24 hours. The short plasma half-life observed *in vivo* is due to clearance from the circulation by hepatic metabolism.

Omeprazole is a racemate and exists in two optical isomers in the S- and R-configuration. The S-isomer generates higher plasma-levels than the R-isomer, due to lower metabolic conversion by hepatic cytochromes (CYP2C19). The active molecular species, the sulphenamide, is non-chiral and equipotent after generation from both isomers. Thus, higher bioavailability and not higher intrinsic activity of the S-isomer (as in esomeprazole) explains the stronger inhibitory action of S-omeprazole observed at the molecular target site inside the parietal cells.

BIOAVAILABILITY

The omeprazole MUPS® tablet (omeprazole magnesium) was an innovative formulation developed in order to offer increased convenience, flexibility and predictability of absorption over omeprazole capsules. MUPS® tablets are small and easily swallowed and can be dispersed in water for people that have trouble swallowing solid forms. Each MUPS® tablet is comprised of about 1,000 individually coated micropellets. The tablet disintegrates rapidly in the stomach and the coated pellets are emptied into the duodenum where the absorption of omeprazole takes place. As previously noted, omeprazole is more stable at the high pH of the duodenum/jejunum, than at the acid pH of the stomach. Studies using gamma scintigraphy confirm that micropellets empty more quickly into the duodenum than single unit dosage forms, particularly in the fed state[4]. This might result in faster bioavailability and therefore longer maintenance of gastric pH at or above pH 4 (the critical threshold for mucosal healing) than would occur with single-unit enteric-coated formulations of the drug.

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Studies comparing the bioavailability of the MUPS® tablet and the conventional capsule were performed after single dose administration of all three strengths, i.e. 10, 20, and 40mg. As the most frequently used dose, 20mg of omeprazole was chosen for a comparison after once daily dosing for six days[5]. All comparisons were performed in healthy male volunteers.

In these studies the area under the plasma concentration vs time curve (AUC) and maximum plasma concentration (Cmax) were evaluated as primary variables for extent and rate of bioavailability. Ninety percent confidence intervals (CI) were constructed for the ratios (tablet/capsule) of the true mean values of AUC and Cmax. Bioequivalence was concluded since the 90% CI for both parameters was entirely within the limits (0.80-1.25) established for bioequivalence (table 1).

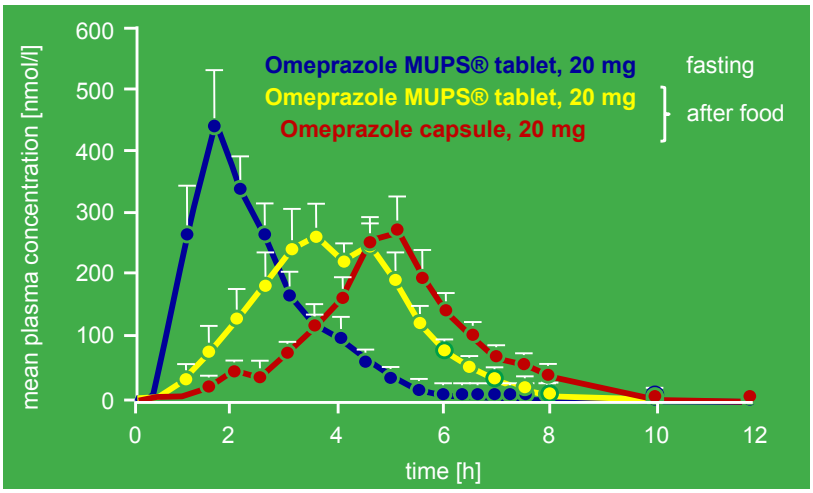
TABLE 1: BIOEQUIVALENCE BETWEEN OMEPRAZOLE MUPS® TABLETS AND OMEPRAZOLE CAPSULES (Adapted from Reference 5).

ratio tabl / caps	10 mg (n = 32)	20 mg (s.d.) (n = 28)	20 mg (r.d.) (n = 28)
AUC			
estimate	1.01	1.02	1.06
(90% CI)	(0.92 – 1.11)	(0.94 – 1.11)	(0.95 – 1.17)
C_{max}			
estimate	1.00	1.05	1.03
(90% CI)	(0.87 - 1.15)	(0.90 - 1.21)	(0.90 – 1.17)

s.d.: single dose; r.d.: repeated dosing (day 6)

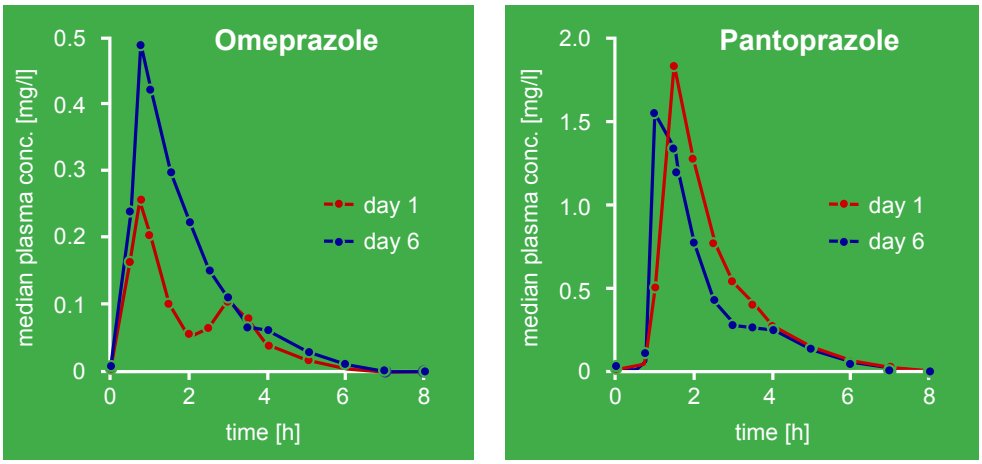
It is notable, however, that the plasma concentration/time curve for both formulations are not identical and are influenced by food intake (Figure 4) with the MUPS® formulation producing faster absorption in the fed state.

FIGURE 4: PLASMA CONCENTRATIONS OF OMEPRAZOLE AFTER 20MG SINGLE DOSE ADMINISTRATION AS MUPS® TABLET OR CAPSULE (Data on file AstraZeneca - reproduced with permission).



Not long after the introduction of the MUPS® tablet, Geus et. al.[6] described the pharmacokinetics of omeprazole MUPS® 20mg compared with pantoprazole 40mg (as single unit enteric-coated tablets) following single (day 1) and repeated (day 6) oral administration and compared the pharmacodynamic effect on gastric pH of both medications on these days (figure 5).

FIGURE 5: MEDIAN PLASMA CONCENTRATIONS OF OMEPRAZOLE MUPS® (20MG) AND PANTOPRAZOLE (40MG) AT DAY 1 AND DAY 6 OF ADMINISTRATION (Adapted from Reference 6).

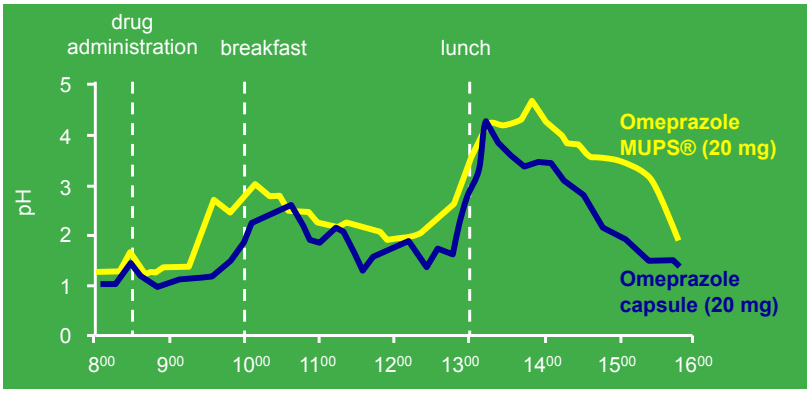


The area under the plasma concentration vs time curve (AUC) and maximum plasma concentration (Cmax) of omeprazole MUPS® (20mg) were slightly higher on day 6 as opposed to day 1 of administration: 74% vs 68% respectively. No pharmacokinetic differences were observed between day 1 and day 6 of administration for pantoprazole. The reasons for this difference, which had been described previously[7], are unclear but it may result from saturation of first pass metabolism and/or a stepwise decrease in gastric acid delivered to the duodenum.

PHARMACODYNAMICS

A placebo-controlled comparison of acid inhibition on the first day of dosing in 18 *Helicobacter pylori*-negative subjects compared 3 proton pump inhibitors (rabeprazole 20mg, lansoprazole 30mg, pantoprazole 40mg) with 20mg omeprazole delivered as capsules or MUPS® tablets[8]. The gastric pH profiles for both dosage forms of omeprazole were similar (figure 6).

FIGURE 6: MEDIAN PH MONITORING PROFILE ON THE FIRST DAY OF PROTON PUMP INHIBITOR TREATMENT - COMPARISON OF OMEPRAZOLE CAPSULE VS MUPS® (Adapted from Reference 8).



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The onset time of antisecretory action, or the first evidence of a statistically significant difference in the median pH values compared with the non-drug period (at 15-minute intervals during the first 6 hours), was 1.25 hours for omeprazole MUPS® tablet and 1.5 hours for omeprazole capsule, 1.75 hours for pantoprazole 40mg tablet and 1.75 hours for rabeprazole 20mg tablet. The authors propose that the differences in the onset of antisecretory action during the first 2 hours following drug administration can be explained by the different rates of absorption of the pro-drugs into the blood. This rate of absorption is related to the galenic formulations used, and absorption from enteric-coated tablet forms, which must first dissolve in the small intestine before absorption occurs, is delayed compared with that from small, individually coated, pellet dosage forms.

In the Geus study[6] (conducted in 16 healthy *Helicobacter pylori*-negative subjects) day 6 median daytime pH was higher with omeprazole MUPS® (20mg) than with pantoprazole (40mg), possibly reflecting the higher bioavailability on repeated daily dosing with the former. However the percentage of time spent above pH 3 and 4 on day 6 was not significantly different between drugs.

SUMMARY

Omeprazole capsules and Omeprazole MUPS® are bioequivalent after single and repeated administration (day 6) at standard doses of 20mg. This bioequivalence is reflected in similar pharmacodynamic effects on gastric pH during the first day after dosing.

In a comparison in healthy subjects, there were no differences in acid inhibitory activity of omeprazole (20mg in a MUPS® tablet) and pantoprazole (40mg) on day 1, but a slightly higher median daytime pH with omeprazole MUPS® (20 mg) at day 6. This is of limited clinical relevance (since the times above pH 3 and 4 were similar for both drugs) but probably reflects the higher bioavailability of omeprazole on day 6 compared to day 1.

CONSUMER STUDIES ON PRILOSEC® OTC (OMEPRAZOLE MUPS® 20 MG) IN THE US

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Of 100,000 adults: 40,000 will suffer reflux symptoms, but only rarely, 20,000 will suffer reflux symptoms weekly, 10,000 will have some grade of esophagitis, 400 will have Barrett's esophagus and 2-4 will develop adenocarcinoma[9]. In the US a poll for the Gallup organisation found that 44% of those surveyed suffered heartburn at least once monthly and 18% took something for indigestion 2 or more times a week.

Recently, it has been proposed that 3 separate disease states represent three increasing degrees of severity on the spectrum of reflux disease: non erosive reflux disease (NERD), gastroesophageal reflux disease (GERD) and Barrett's esophagus[10]. Most people with even

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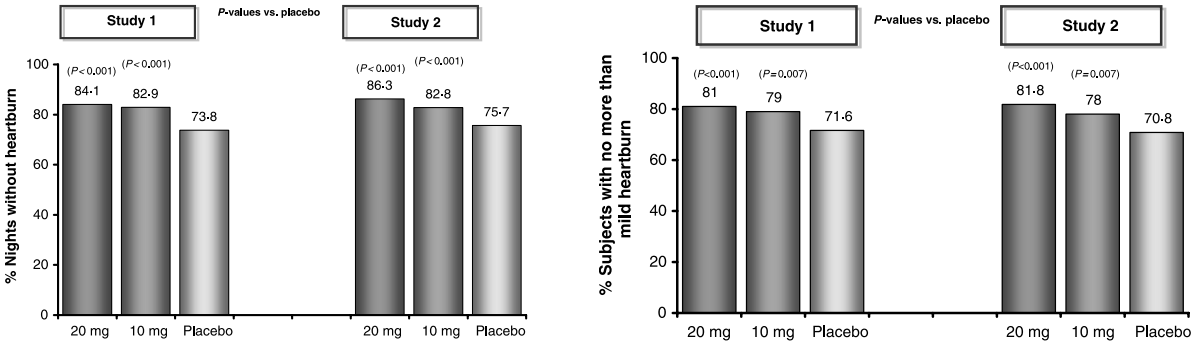
frequent heartburn do not have erosive disease on endoscopy, and in the absence of 'alarm' signs or symptoms (e.g. weight loss, dysphagia or anaemia), empirical treatment with a PPI is now recommended. Only if response to a PPI is inadequate, should endoscopy be considered.

For frequent sufferers, complete and long-lasting relief of frequent heartburn is the requirement most frequently identified in consumer research.

In the US, omeprazole has been available 'over the counter' from drug stores since 2003. The recommended dose is a 20mg (20.6 mg omeprazole magnesium) MUPS® tablet daily for 14 days in people with frequent symptoms (2 or more days of heartburn per week).

The efficacy of this regimen in the target group was demonstrated in two multi-centre, double-blind placebo controlled randomised clinical studies of identical design[11]. A total of 3162 subjects were randomised to omeprazole MUPS® 20mg, omeprazole MUPS® 10mg or matching placebo (study 1: 523 MUPS® 20; 518 MUPS® 10; 519 placebo and study 2 524 MUPS® 20; 520 MUPS® 10; 520 placebo) and kept a diary for the 14 days of treatment. One day after the first dose, nearly 50% of subjects receiving MUPS® 20 reported no heartburn. Across both studies subjects on MUPS® 20 reported around 85% of nights as completely heartburn free over the 14 days of the study (P < 0.001 vs placebo) and suffered no more than mild heartburn on around 80% of the daytime periods. (Figure 7).

FIGURE 7 (Adapted from Reference 11).



Both omeprazole doses were significantly more effective than placebo on days 1 and 14 for percentage of subjects heartburn-free for 24 hours (P < or = 0.003), and across all 14 days for percentage of heartburn-free days (P < 0.001). The authors concluded that this degree of efficacy and the good tolerability evident in the study, confirmed omeprazole MUPS® 20mg as an excellent choice for self care of frequent heartburn.

In the US, OTC status means that individuals can self–select treatments from drug store shelves and must rely on the product label to guide correct use of the medicine. Often studies are performed to demonstrate that the product label achieves the purpose of appropriate selection and usage of the drug according to the label restrictions in place. Such a naturalistic 'actual

use' study was reported by Fendrick *et al* in 2004[12]. In this 3 month observational study 1999 subjects with heartburn were exposed to the product in a 'shopping mall' environment; of these 866 purchased the medicine. A high proportion of this number (88%) returned a diary for analysis. The aims of the study were to answer the following questions:

- Do consumers correctly self-select to use omeprazole?
- Do consumers comply with the product label (14 days of once-daily dosing)?
- Do consumers use more than 14 doses of medication only under the advice of a physician?

Subjects accurately self-selected themselves as frequent sufferers: more than 90% of participants had heartburn 2 or more days/week. Diary data demonstrated a high degree of compliance to label directions and only 3% of subjects took more than 14 doses without consulting a physician. After 3 months, 43% of subjects did not have recurrence of their heartburn, confirming that a 14 day treatment with omeprazole can have lasting effects in this patient population. The majority (75%) of subjects had contact with a physician about heartburn before, during, or soon after the study (26% during the 3-month study). Therefore, at least in the US, frequent heartburn is most often not treated completely without advice. Since a trial of empirical PPI treatment is the most likely outcome of consultation, this seems an acceptable pattern of usage when there are no 'alarm' symptoms present and response is satisfactory.

Lansoprazole at a dose of 15mg is now available OTC in the US for the same indication as omeprazole MUPS® 20 (omeprazole magnesium 20.6mg). Recently the pharmacodynamics of these doses have been compared in a 3 period, double blind, cross over design study of 24 hours steady state gastric acid suppression (on day 5 of dosing) in 40 healthy volunteers[13]. The primary efficacy variable was the percentage time intragastric pH was >4.0 over 24 hours on day 5 of dosing.

The mean (SE) percentage time pH was >4.0 was 45.7% (3.45%) for omeprazole MUPS® 20.6mg and 36.8% (3.45%) for lansoprazole 15mg, an absolute difference of 8.9% ($P < 0.0001$), and a relative difference of 24.2%. Figure 8 shows the distribution of subject treatment ratios for the percentage time pH >4.0 in 24 hours.

SUMMARY

Omeprazole magnesium formulated as MUPS® tablets is available for self selection in US drugstores for individuals with frequent heartburn. Studies confirm the good performance of omeprazole MUPS® 20mg in producing complete relief of heartburn during 14 days of treatment. A large 'actual use' study mimicking the OTC setting, confirmed that individuals were able to appropriately select themselves as suitable for the treatment and very few (3%) exceeded 14 days treatment without a doctor's advice. Finally comparison with a recently approved competitor PPI (lansoprazole 15mg) confirms statistically greater acid suppression at steady state (day 5) with omeprazole MUPS® 20mg.

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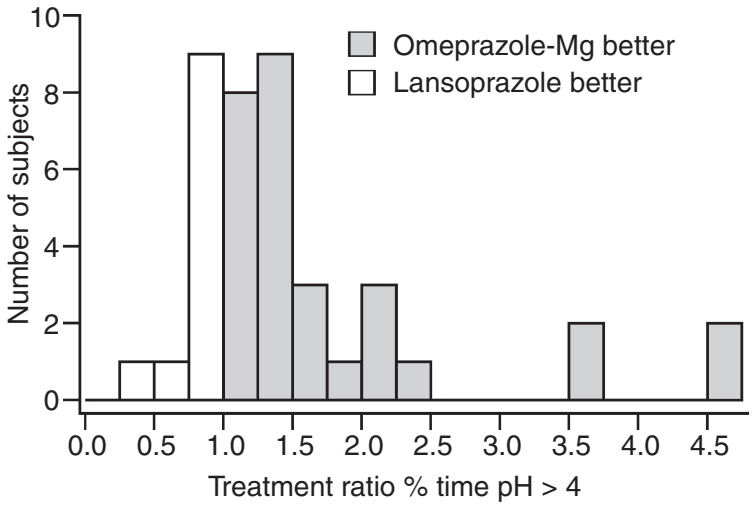
FIGURE 8 (Adapted from Reference 13).



Distribution of within subject treatment ratios for the percentage time pH>4.0 in 24 h (ie. percentage time for omeprazole-Mg / percentage of time for lansoprazole). For 29 subjects, the ratio was >1 (i.e. the percentage time pH >4 was greater for omeprazole-Mg than for lansoprazole). For 10 subjects, the ratio was <1. (i.e. percentage time pH >4 was less for omeprazole-Mg than for lansoprazole). In one subject the response was equal.

CLINICAL EFFICACY OF OMEPRAZOLE MUPS® IN THE NETHERLANDS AND SOME CONSIDERATIONS RELATING TO GENERIC SUBSTITUTION – Prof. Chris J.J. Mulder, MD PhD

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SYMPTOMATIC EFFICACY OF PPIS IN THE TREATMENT OF REFLUX ESOPHAGITIS

Proton pump inhibitors (PPIs) have proved to be effective in treating reflux oesophagitis and healing erosive disease. However relatively few studies have compared the symptomatic efficacy of PPIs directly in such patients. A double blind multicentre study in the Netherlands[14] randomised patients with symptomatic grade I-IV reflux oesophagitis to omeprazole MUPS® 20mg, lansoprazole 30mg and pantoprazole 40mg, all dosed daily in the morning.

Patient satisfaction and symptoms were evaluated after 4 and 8 weeks. Patients not satisfied after 8 weeks were treated for another 4 weeks with omeprazole 40mg MUPS® (open). Successful treatment was followed by 3 months of maintenance treatment with omeprazole MUPS® 20mg (in patients satisfied after 4 or 8 weeks) or omeprazole MUPS® 40mg (patients satisfied after 12 weeks).

On intention-to-treat analysis (n = 461) at 4 and 8 weeks, respectively, 84% and 87% (omeprazole MUPS®), 78% and 81% (lansoprazole), and 84% and 89% (pantoprazole) were free of heartburn. These results were reflected in ratings of patient satisfaction with treatment after 4 and 8 weeks, and this was similar in all treatment groups. During maintenance, 87% in the omeprazole MUPS® 20mg group and 81% in the omeprazole MUPS® 40mg group were satisfied after 3 months.

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Omeprazole MUPS® 20mg and pantoprazole 40mg have similar efficacy in the treatment of reflux oesophagitis. Based on patient satisfaction, all three drugs in this study were equally effective at these doses.

SOME CONSIDERATIONS RELATING TO GENERIC SUBSTITUTION OF PPIS

Proton pump inhibitors are the most effective acid suppressive drugs. They are widely used for gastroesophageal reflux disease, ulcer disease, anti-H.pylori therapy, and as protective agents when chronic NSAID therapy is needed. Surveys of usage have shown substantial growth in recent years and the cost of this in turn creates pressure to use the least expensive drugs. Since 2004, when the patent expired for omeprazole, more than 50 generic preparations have been launched in the Netherlands.

To be launched as a generic equivalent to the originator drug, a formulation has to show bioequivalence according to a standardised definition. The area under the plasma concentration vs time curve (AUC) and maximum plasma concentration (Cmax) are evaluated as primary variables for extent and rate of bioavailability. Ninety percent confidence intervals (CI) are constructed for the ratios (generic vs originator) of the true mean values of AUC and Cmax. Bioequivalence can be concluded if the 90% CI is entirely within the limits (0.80-1.25) established as representing effective bioequivalence. As long as this condition is met, generics can differ with respect to pharmaceutical form (pills, capsules, pellets, salts and excipients), pattern of bioavailability, and pharmacokinetics. When, as with omeprazole, the delivery of a pro-drug to the site of activation is crucially dependant on properties such as gastroresistance of the formulation, differences in clinical effect are plausible for different galenic forms of the same drug. Studies examining dissolution of formulations in a pH of 1 and 3 (pH in the stomach) and dissolution in a pH of 6.8 (pH in the small intestine) after prior exposure to low pH, confirm that not all behave in the same way[15]. Although ultimately all products may release the same amount of active compound, the pattern of release varies markedly and 'dose dumping' can occur when drug is released very quickly.

Not all proton pumps are activated at the same moment, but an activated proton pump is required for the protonation of the pro-drug. Only the activated pro-drug can block the proton pump. Hence 'dose dumping' will result in blockage of only a small number of pumps that are active while the majority of the pro-drug may leave the body without any effect on the "sleeping" or currently inactivated proton pumps.

Bio-equivalency is based on static numbers retrieved from experiments with healthy volunteers, often after one dose of the active compound. However pharmacodynamic effects may vary over time, for example in relation to changes in bioavailability with multiple dosing, as has been observed with omeprazole[6]. Ultimately, the only way to evaluate the efficacy of an active compound is to study clinical outcome parameters. Typically only the originator drug is studied extensively with regard to pharmacodynamic effect and clinical efficacy. Comparisons between

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originator and generic products are only valid for the formulation chosen, and with multiple generic forms available, such comparisons have limited utility and so are seldom performed.

In a survey of generic drug usage in the Netherlands, amongst 5254 users of generic omeprazole 7.9% switched to Losec® and 11.7% switched to another PPI because of lack of or unsatisfactory efficacy[15]. In contrast, in a 'control' group only 1.1% of patients on generic paroxetine needed to be switched to Seroxat®. Thus approximately 20% of individuals did not appear to achieve a satisfactory response on generic omeprazole. This lack of a predictable response has the potential to increase the hidden costs associated with increased consultations and the endoscopies that might result.

SUMMARY

Omeprazole MUPS® 20mg provided effective symptomatic relief equivalent to the newer PPIs lansoprazole 30mg and pantoprazole 40mg in patients with grade I-IV reflux oesophagitis treated for 4-8 weeks.

Surveys of generic omeprazole usage in the Netherlands suggest a relatively high level of dissatisfaction (around 20%) requiring substitution by the originator product or an alternative PPI. This in turn suggests that some usage of generic omeprazole represents a false economy and may result in increased hidden costs. Many factors influence the availability of omeprazole at the site of its activation and this can be profoundly influenced by the formulation of the drug for oral delivery. With this drug in particular, a limited definition of bioequivalence on pharmacokinetic grounds may not predict pharmacodynamic and clinical response adequately. In the absence of pharmacodynamic and clinical evaluations of generic formulations, health care professionals should not assume that all omeprazole formulations are the same and they may want to advise consumers purchasing OTC drugs accordingly.

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