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# Drug Interaction Studies with Dexlansoprazole Modified Release (TAK-390MR), a Proton Pump Inhibitor with a Dual Delayed-Release Formulation

## Results of Four Randomized, Double-Blind, Crossover, Placebo-Controlled, Single-Centre Studies

*Majid Vakily, Ronald D. Lee, Jingtao Wu, Lhanoo Gunawardhana* and *Darcy Mulford*

Research and Development, Takeda Global Research and Development Center, Inc., Deerfield, Illinois, USA

## Abstract

**Background and objective:** Most proton pump inhibitors are extensively metabolized by cytochrome P450 (CYP) isoenzymes, as are many other drugs, giving rise to potential drug-drug interactions. Dexlansoprazole modified release (MR) [TAK-390MR] is a modified-release formulation of dexlansoprazole (TAK-390), an enantiomer of lansoprazole, which employs an innovative Dual Delayed Release™ technology designed to prolong the plasma dexlansoprazole concentration-time profile following once-daily oral administration. As with lansoprazole, dexlansoprazole is metabolized mainly by CYP3A and CYP2C19. Based on *in vitro* studies, dexlansoprazole has the potential to inhibit activity of these isoenzymes and also may induce human hepatic CYP1A and CYP2C9 activity. To determine whether dexlansoprazole has an effect on these isoenzymes *in vivo*, drug interaction studies with dexlansoprazole MR were conducted.

**Methods:** Four separate randomized, double-blind, two-way crossover, placebo-controlled, single-centre studies were conducted in healthy volunteers to evaluate the effect of dexlansoprazole on the pharmacokinetics of four test substrates (diazepam, phenytoin, theophylline [administered as intravenous aminophylline] and warfarin), which were selected based on *in vitro* and/or *in vivo* data that suggest a potential drug interaction with CYP isoenzymes or potentially coadministered narrow therapeutic index drugs. In each study, dexlansoprazole MR 90 mg or placebo was administered once daily for 9 or 11 days in each period. Subjects received a single dose of test substrate in each study period. Pharmacokinetic parameters of the test substrates were estimated using noncompartmental methods. A conclusion of no effect of dexlansoprazole MR on the test substrate was made if the 90% confidence intervals (CIs) for the ratios of the central values for the observed maximum plasma drug concentration ($C_{max}$) and the area under the plasma concentration-time curve (AUC) of test substrate administered with

dexlansoprazole MR versus placebo were within 0.80–1.25 based on an analysis of variance model. The potential for a pharmacodynamic interaction was also assessed for warfarin using prothrombin time, measured as the international normalized ratio. Routine safety assessments were conducted in these studies.

**Results:** Mean $C_{max}$ and AUC values were generally similar for each test substrate when administered with multiple once-daily doses of dexlansoprazole MR or placebo. The 90% CIs for the bioavailability of these test substrates administered with dexlansoprazole MR relative to that obtained when the substrates were administered with placebo were within the bioequivalency range of 0.80–1.25, indicating that multiple doses of dexlansoprazole MR had no effect on the pharmacokinetics of these drugs. Additionally, dexlansoprazole MR had no effect on the pharmacodynamics of warfarin. Administration of these drugs with dexlansoprazole MR 90 mg or placebo was well tolerated; the only serious adverse event, which led to a subject's discontinuation from the study, was considered unrelated to study drugs.

**Conclusions:** Coadministration of dexlansoprazole MR with diazepam, phenytoin or theophylline did not affect the pharmacokinetics of these drugs, and therefore is unlikely to alter the pharmacokinetic profile of other drugs metabolized by CYP2C19, CYP2C9, CYP1A2 and perhaps CYP3A. Additionally, dexlansoprazole MR coadministered with warfarin did not affect the pharmacokinetics of the warfarin enantiomers and had no effect on the anticoagulant activity of warfarin. Dexlansoprazole MR was well tolerated in these trials of healthy subjects.

## Background

Proton pump inhibitors (PPIs) are used extensively in the management of gastro-oesophageal reflux disease (GORD). Effective GORD management generally requires long-term therapy,[1] increasing the likelihood that PPIs will be taken in combination with other drugs. PPIs have the potential to interact with other drugs via several mechanisms, the most important of which is competitive inhibition of the hepatic cytochrome P450 (CYP) isoenzymes involved in the metabolism of these drugs.[2]

As with many drugs, currently marketed PPIs undergo hepatic metabolism involving multiple CYP isoenzymes, particularly CYP3A and polymorphic CYP2C19.[2-5] The affinity of PPIs for hepatic CYP isoenzymes is drug specific and determines their ability to affect the metabolism of other drugs that are substrates for these isoenzymes.[2,3] Few drug interactions have been associated with some PPIs, such as lansoprazole, pantoprazole and rabeprazole, presumably because of their low affinity for certain hepatic CYP isoenzymes or clearance through alternative pathways, e.g. nonenzymatic reduction in the case of rabeprazole.[2,4,6,7] However, omeprazole is rapidly and extensively metabolized by CYP3A and CYP2C19[3] and has been shown in well controlled studies to reduce the clearance of drugs such as diazepam (by 25% to >50%, depending on dose)[8,9] and phenytoin (by approximately 15%).[10] Similar results have been found in studies of esomeprazole (an enantiomer of omeprazole) and diazepam.[11]

The population at risk for experiencing drug interactions is substantial. In the US, two large retrospective studies showed that 10–58% of patients taking PPIs were also receiving potentially interacting concurrent medication.[12,13] Risks may be especially high in the elderly, who tend to have multiple co-morbid conditions and more polypharmacy, as well as in patients taking medications with a narrow therapeutic index.[7,14] Warfarin is of particular con-

cern since it is widely prescribed, especially in the elderly, and has a narrow therapeutic index. Warfarin-associated drug interactions are common,[15] and PPI product labels warn of the possibility of changes in prothrombin time in patients taking concomitant warfarin/PPI therapy.[11,16-20] Drug interactions with warfarin can have severe and even life-threatening consequences. It is therefore important for clinicians to exercise caution in selecting medications for the safe management of individual patients.

Dexlansoprazole modified release (MR) is a novel formulation of dexlansoprazole, an enantiomer of lansoprazole. Dexlansoprazole MR employs an innovative delivery system with Dual Delayed Release™ technology designed to prolong the plasma dexlansoprazole concentration-time profile and provide extended duration of acid suppression.[21] Dexlansoprazole and lansoprazole are primarily metabolized by CYP3A and CYP2C19. *In vitro* data suggest that dexlansoprazole and lansoprazole have the potential to inhibit the activity of CYP3A and CYP2C19 and, in the case of dexlansoprazole, the potential to induce CYP2C9.[22] Additionally, an *in vitro* study has shown that omeprazole may also induce human hepatic CYP1A.[23] Furthermore, an *in vivo* study has demonstrated a slight potential for induction of CYP1A by lansoprazole.[16,24] It is therefore relevant to investigate the effect of dexlansoprazole MR on the metabolism of drugs metabolized by these different isoenzymes.

This article presents the results of four separate studies investigating the effect of dexlansoprazole MR 90 mg (the highest dose used in phase III evaluations) on the pharmacokinetics of diazepam, phenytoin, theophylline and warfarin, all of which are test substrates for the CYP isoenzymes that may potentially be affected by dexlansoprazole. In addition, the effect of dexlansoprazole MR on the pharmacodynamics of warfarin was assessed.

## Selection of Study Drugs

The selection of test substrates was based on one or more of the following: involvement of CYP3A and/or CYP2C19 in its metabolism, availability of *in vitro* and/or *in vivo* evidence that dexlansoprazole may affect its pharmacokinetics (e.g. inhibition or induction of CYP1A or CYP2C9), and/or a narrow therapeutic index drug with the potential for concomitant administration with dexlansoprazole MR.

Diazepam is used widely in the treatment of anxiety, insomnia, seizures and other disorders. Its metabolism is mainly mediated by CYP3A and CYP2C19, whereas the metabolism of its major circulating metabolite (nordiazepam) is mediated by CYP2C19.[25] Clinical studies have shown that PPIs, e.g. omeprazole and esomeprazole, can reduce the clearance of diazepam.[8-10,26] Hence, diazepam was selected as a test substrate to investigate the effect of multiple once-daily doses of dexlansoprazole MR 90 mg on CYP3A and CYP2C19 activity. Quantitation of plasma nordiazepam allows direct assessment of the effect of dexlansoprazole on the *in vivo* activity of CYP2C19.

Phenytoin is an antiepileptic agent with a narrow therapeutic index and nonlinear kinetics; its metabolism involves CYP2C19 and CYP2C9.[27,28] CYP2C9 mediates 4-hydroxylation of phenytoin, and recent *in vitro* studies have shown that CYP2C9 is activated by dexlansoprazole.[22] Induction or inhibition of the CYP isoenzymes responsible for phenytoin metabolism may have a marked effect on phenytoin plasma concentrations.[27]

Theophylline, a bronchodilator used in the treatment of asthma, has a narrow therapeutic index such that changes in the pharmacokinetics of theophylline can result in toxicity or therapeutic failure. Its metabolism is primarily mediated by CYP1A2.[29] Induction of this isoenzyme could potentially decrease plasma concentrations of theophylline, causing therapeutic failure.

Warfarin is the most commonly used oral anticoagulant. It is widely prescribed in patients at risk for thromboembolic events, including the elderly. It is characterized by a narrow therapeutic index, wide variability in dose requirements among individual patients, and high susceptibility to drug-drug interactions.[30-32] The clinical implications of drug interactions with warfarin are potentially serious. Those that enhance warfarin activity may cause haemorrhage, whereas those that diminish activity may

cause therapeutic failure.[32] Therefore, it is important to ensure that both the pharmacokinetics and pharmacodynamics of warfarin are not affected by concomitantly administered drugs. Warfarin is a 50 : 50 racemic mixture of *R*- and *S*-warfarin, with the *S*-enantiomer being pharmacologically more potent. The *S*-enantiomer is a substrate for CYP2C9, whereas metabolism of the *R*-enantiomer is mediated mainly by CYP3A, CYP2C19 and CYP1A2.[31] The pharmacodynamics of warfarin can be readily assessed using prothrombin time, measured as the international normalized ratio (INR).

## Methods

Four separate studies with nearly identical study designs were conducted in healthy volunteers to assess the effect of once-daily administration of dexlansoprazole MR on the pharmacokinetics of diazepam, phenytoin, theophylline and warfarin. In the warfarin study, the effect of dexlansoprazole MR on warfarin pharmacodynamics measured as INR was also evaluated.

### Subjects

Between 16 and 20 healthy subjects participated in each of the four studies. Eligible subjects included healthy male and female volunteers aged 18–55 years. In each study, the health status of subjects was confirmed by routine laboratory tests, vital signs, ECG examinations, medical history and physical examination before enrolment in the study. Inclusion criteria included a body mass index of 18–30 kg/m$^2$. Female subjects must have had a negative pregnancy test, be using an approved method of contraception, and not be lactating.

Exclusion criteria included gastrointestinal disease that would be expected to influence the absorption of drugs; a positive test result for hepatitis B surface antigen, hepatitis C virus, or HIV antibody; use of caffeine, nicotine, alcohol or grapefruit juice; use of concomitant prescription (e.g. erythromycin, cimetidine) or over-the-counter medications (e.g. vitamins, dietary supplements). In addition, subjects were excluded from the warfarin study if they had an INR level >1.2 on day 1 of period 1 before dosing or if they were premenopausal.

### Study Designs

Each of the four studies was a randomized, double-blind, two-way crossover, placebo-controlled, single-centre study designed to assess the effect of multiple once-daily administration of dexlansoprazole MR on the pharmacokinetics of test substrates (diazepam, phenytoin, theophylline and warfarin). Additionally, the effects of dexlansoprazole MR on the pharmacodynamics of warfarin were evaluated. Each study protocol was approved by a regional Institutional Review Board. All subjects gave written informed consent before any study-related procedure was initiated.

In each study, subjects were randomized according to schedules generated by the Statistics Department at Takeda Pharmaceutical Company Limited to one of two sequence groups, which determined the order in which the subjects received the multiple doses of dexlansoprazole MR or placebo. Dexlansoprazole MR and placebo were manufactured by Takeda Pharmaceutical Company Limited (Osaka, Japan) and were supplied in size 0, gray opaque capsules that were identical in size, shape and colour. Dexlansoprazole MR and placebo clinical supplies were packaged and labelled by Fisher Clinical Services (Mount Prospect, IL, USA) on behalf of Takeda. Whether a subject received dexlansoprazole MR or placebo in period 1 or 2 of each study was not known by the investigator, the subject, or the pharmacist. Subjects received a single open-label dose of the test substrate in each period determined by the study in which the subject was enrolled. Details of the study designs, including drug administration days for each test substrate, appear in table I.

### Drug Administration

Dexlansoprazole MR or placebo was administered once daily for 9 or 11 days in each period of the trial. Dosing (dexlansoprazole MR or placebo) began at approximately 8:00am in each study following a minimum 10-hour fast on each dosing day. A single dose of the test substrate (oral diazepam

**Table I.** Study designs

| Test substrate | No. of subjects enrolled | Duration of each treatment period (days) | Interval between periods[a] (days) | Test substrate coadministered with dexlansoprazole MR or placebo (day) | Duration of PK sampling after administration of test substrate (hours) |
|---|---|---|---|---|---|
| Oral diazepam 5 mg | 20 | 11 | ≥7 | 6 | 0–144 |
| Oral phenytoin 250 mg | 16 | 9 | ≥7 | 6 | 0–96 |
| Single IV infusion aminophylline 400 mg (theophylline 315 mg) | 20 | 9 | ≥10 | 8 | 0–48 |
| Oral warfarin 25 mg | 19 | 11 | ≥10 | 6 | 0–144 |

a This allowed for an actual washout interval for the test substrate of ≥13 days (or approximately 4–5 half-lives) depending on whether the test substrate was administered on day 6 or 8.

**IV** = intravenous; **MR** = modified release; **PK** = pharmacokinetics.

5 mg, phenytoin 250 mg, warfarin 25 mg, or intravenous aminophylline 400 mg equivalent to theophylline 315 mg) was also administered at approximately 8:00am on day 6 or day 8 of each period (table I). A minimum interval of at least 7 days was provided between the last dose of dexlansoprazole MR or placebo in the first period and the first dose of dexlansoprazole MR or placebo in the second period. This allowed for an actual washout interval for the test substrate of at least 13 days or approximately 4–5 half-lives, as a single dose of these test substrates was given on day 6 or 8 of each period.

### Sample Analysis

Serial blood samples were obtained from predose to 96 hours postdose for phenytoin and predose to 144 hours postdose for diazepam and warfarin on day 6 of each period. Serial blood samples were collected for quantitation of theophylline plasma concentrations from predose to 48 hours postdose on day 8 of each period. Blood was collected into EDTA Vacutainer® tubes and the plasma separated and stored at –20ºC until assayed.

Plasma samples were analysed for diazepam and its nordiazepam metabolite using a validated liquid chromatography assay with tandem mass spectrometric detection (LC-MS/MS) by Covance Bioanalytical Services, Indianapolis, IN, USA, with a lower limit of quantitation (LLQ) of 1.00 ng/mL for both analytes based on a sample volume of 0.1 mL. The method was precise and accurate with quality control samples having inter-batch precision (coefficient of variation) and accuracy of ≤6.0% and 94.0–106.7%, respectively, for diazepam and ≤4.9% and 94.3–105.3%, respectively, for nordiazepam.

Plasma concentrations of phenytoin were determined by a validated LC-MS/MS method at Cedra Corporation, Austin, TX, USA, with an LLQ of 10.0 ng/mL using a 0.200 mL sample volume. Quality control samples showed the method to be precise and accurate, with interday precision of ≤6.9% and accuracy of 98–102%.

Plasma concentrations of theophylline were determined by a validated LC-MS/MS method at Prevalere Life Sciences, Whitesboro, NY, USA,

with an LLQ of 200 ng/mL using a 0.05 mL sample volume. Quality control samples showed the method to be precise and accurate, with interday precision of ≤8.0% and accuracy of 102–106%.

Plasma concentrations of *R*- and *S*-warfarin were determined simultaneously by a validated LC-MS/MS method at Covance Bioanalytical Services, Indianapolis, IN, USA, with an LLQ of 5.00 ng/mL using a 0.250 mL sample volume. Quality control samples showed the method to be precise and accurate, with interday precision of ≤8.1% for *R*-warfarin and ≤6.2% for *S*-warfarin. The accuracy of the method was 97–100% for *R*-warfarin and 95–99% for *S*-warfarin.

Since the metabolism of these substrates involves CYP2C19 and/or CYP2C9, which are highly polymorphic, genotyping of the *CYP2C9* and *CYP2C19* genes was conducted to determine the metabolizer status of each subject in order to help explain any potential aberrant values. On day 1 of the dosing period 1, a single blood sample per subject was collected into an EDTA Vacutainer® tube and stored at –20ºC before DNA extraction for genotyping of *CYP2C9* (*2 and *3) and *CYP2C19* (*2, *3, *4 and *5) genes (Cogenics, Morrisville, NC, USA). The *CYP2C19* and *CYP2C9* genotyping was based on a polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method. Briefly, the methodology employed for *CYP2C19* and *CYP2C9* genotyping involved amplification using purified genomic DNA samples, gel electrophoresis and photographic recording of the base pair fragments under UV light.

### Pharmacokinetic Evaluations

The pharmacokinetic parameters of the test substrate in each study were estimated by noncompartmental methods using WinNonlin Professional Version 4.1 (Pharsight Co, Mountain View, CA, USA). The observed maximum plasma drug concentration ($C_{max}$) and the time to maximum drug concentration ($t_{max}$) were obtained directly from the plasma concentration-time profile for each subject. The apparent terminal elimination rate constant ($\lambda_z$) was estimated using least squares regression analysis of the terminal log-linear portion of the plasma concentration-time profiles. The apparent terminal-phase elimination half-life ($t_{½z}$) was calculated as $\ln(2)/\lambda_z$. The area under the plasma concentration-time curve (AUC) from time zero to the last quantifiable concentration ($AUC_t$) was calculated by the linear trapezoidal rule. The extrapolated AUC from t to infinity ($AUC_{t-\infty}$) was estimated by dividing the observed $C_t$ by the estimated $\lambda_z$. The AUC from time zero to infinity ($AUC_\infty$) was calculated as the sum of $AUC_t$ and $AUC_{t-\infty}$.

### Pharmacodynamic Evaluation of Warfarin

The pharmacodynamics of warfarin were assessed by prothrombin time, which was measured and reported as the INR. Pharmacodynamic assessments of warfarin included area under the INR versus time curve from 0 to 144 hours ($INR_{144}$) and maximum INR ($INR_{max}$) over 144 hours following warfarin dosing on day 6.

### Safety Evaluation

Safety was monitored in all studies through adverse event reports, concomitant medication use, 12-lead ECGs, physical examination, vital sign assessments and laboratory evaluations (haematology, urinalysis, clinical chemistry). Any clinically significant change in a laboratory value was to be reported by the investigator as an adverse event.

### Statistical Analysis

The descriptive statistics for the pharmacokinetic parameters are expressed as means ± SD. The effects of dexlansoprazole MR on the test substrates were assessed in each study by point estimates and 90% confidence intervals (CIs) for the ratios of the central values for the $C_{max}$ and AUC values of diazepam and its metabolite nordiazepam, phenytoin, theophylline, *R*- and *S*-warfarin using an ANOVA model with factors of sequence, subject within sequence, period and regimen. The subject-within-sequence factor was random, while the other three factors were fixed. A conclusion of 'no effect' (i.e. no drug-drug interaction) was made within each study if the 90% CIs for the ratio of the central

values between test substrate administered with dexlansoprazole MR and test substrate administered with placebo regimens were within the 'no effect' range defined as 0.80 to 1.25 for $C_{max}$ and AUC. INR parameters were summarized using descriptive statistics and analysed using the same ANOVA model.

### Sample Sizes

#### *Diazepam*

A sample size of 20 subjects, with equal number of subjects in each of the two sequences, was used in the diazepam interaction study. This sample size allowed for up to four discontinuations (20% discontinuation rate) and still provided at least 90% probability of concluding no effect (no interaction) of dexlansoprazole on diazepam AUC if the true difference in diazepam AUC central values between the dexlansoprazole MR and placebo regimens was no more than 5%. The sample size was calculated using 0.022 as the intrasubject variance for the natural logarithm of diazepam AUC, which was determined from the literature.[33]

#### *Phenytoin*

A sample size of 16 subjects, with an equal number of subjects in each of the two sequences, allowed for up to four discontinuations (approximately 25% discontinuation rate) and still provided at least 95% probability of concluding no effect (no interaction) of dexlansoprazole on phenytoin AUC if the true difference in phenytoin AUC central values between the dexlansoprazole MR and placebo regimens was no more than 5%. The sample size was calculated using 0.012 as the intrasubject variance for the natural logarithm of AUC, which was determined from the literature.[34]

#### *Theophylline*

A sample size of 20 subjects, with an equal number of subjects in each of the two sequences, was used in the theophylline interaction study. This allowed for up to four discontinuations (20% discontinuation rate) and still provided at least 95% probability of concluding no effect (no interaction) of dexlansoprazole on theophylline AUC if the true difference in theophylline AUC central values between the dexlansoprazole MR and placebo regimens was no more than 5%. The sample size was calculated using 0.011 as the intrasubject variance for the natural logarithm of AUC, which was determined from the literature.[35]

#### *Warfarin*

A sample size of 20 subjects, with an equal number of subjects in each of the two sequences, was used in the warfarin interaction study. This allowed for up to four discontinuations (approximately 20% discontinuation rate) and still provided at least 90% probability of concluding no effect (no interaction) of dexlansoprazole on *S*-warfarin $C_{max}$ if the true difference in *S*-warfarin $C_{max}$ central values between the dexlansoprazole MR and placebo regimens was no more than 5%. For *S*-warfarin AUC, *R*-warfarin $C_{max}$ and AUC, and the pharmacodynamic parameters of warfarin, this probability was greater. The sample size was calculated using 0.023 as the intrasubject variance for the natural logarithm of *S*-warfarin $C_{max}$, which was determined from a previous study examining drug interactions with warfarin and a different investigational drug.[36]

## Results

### Diazepam

#### *Baseline Demographics and Disposition of Subjects*

The effect of multiple once-daily doses of dexlansoprazole MR 90 mg on the pharmacokinetics of a single oral dose of diazepam 5 mg was assessed in 20 healthy individuals. Eighty-five percent of the subjects were White, 15% were Black, and most were men (65%). Subjects ranged in age from 20 to 48 years (mean ± SD: 29.6 ± 8.3 years at baseline). Mean height was 175.9 ± 7.7 cm, and mean weight was 78.6 ± 9.5 kg. Of the 20 subjects enrolled, 19 completed both regimens and were included in the pharmacokinetic analyses. All subjects were included in the safety analysis. All but

**Table II.** Summary of pharmacokinetic parameter estimates of test substrates administered concomitantly with dexlansoprazole modified release (MR) or placebo. Data are expressed as means ± SD

| Regimen | $t_{max}$ (h) | $C_{max}$ (ng/mL) | $AUC_t$ (ng • h/mL) | $AUC_\infty$ (ng • h/mL) |
|---|---|---|---|---|
| **Diazepam (n = 19)** | | | | |
| Diazepam + dexlansoprazole MR | 0.91 ± 0.41 | 165.82 ± 38.86 | 3473.56 ± 936.74 | 4395.43 ± 1705.51 |
| Diazepam + placebo | 0.75 ± 0.37 | 186.05 ± 53.61 | 3388.61 ± 863.54 | 4047.62 ± 1262.22 |
| Nordiazepam + dexlansoprazole MR | 83.36 ± 36.31 | 20.64 ± 6.62 | 2217.24 ± 551.21 | ND |
| Nordiazepam + placebo | 74.54 ± 28.98 | 21.48 ± 6.68 | 2350.33 ± 554.17 | ND |
| **Phenytoin (n = 16)** | | | | |
| Phenytoin + dexlansoprazole MR | 7.56 ± 5.33 | 2.85 ± 0.61 | 111.90 ± 27.04 | 113.99 ± 28.53 |
| Phenytoin + placebo | 9.16 ± 5.42 | 2.92 ± 0.60 | 113.41 ± 26.18 | 115.62 ± 27.71 |
| **Theophylline (n = 19)** | | | | |
| Aminophylline + dexlansoprazole MR | 0.69 ± 0.18 | 12 350 ± 3106 | 122 300 ± 28 680 | 126 500 ± 29 230 |
| Aminophylline + placebo | 0.65 ± 0.15 | 11 660 ± 2572 | 126 600 ± 28 430 | 131 800 ± 30 290 |
| **Warfarin (n = 18)** | | | | |
| *S*-warfarin + dexlansoprazole MR | 0.67 ± 0.25 | 1720 ± 295 | 50 110 ± 11 381 | 54 540 ± 13 943 |
| *S*-warfarin + placebo | 0.95 ± 0.45 | 1580 ± 248 | 47 920 ± 10 096 | 51 760 ± 12 334 |
| *R*-warfarin + dexlansoprazole MR | 1.03 ± 1.75 | 1650 ± 254 | 73 030 ± 10 481 | 85 070 ± 15 860 |
| *R*-warfarin + placebo | 1.76 ± 3.57 | 1520 ± 203 | 71 050 ± 10 166 | 82 150 ± 14 618 |

**AUC** = area under the plasma concentration-time curve; **$AUC_\infty$** = AUC from time zero to infinity; **$AUC_t$** = AUC from time zero to the time of last quantifiable sampling time point; **$C_{max}$** = observed maximum plasma drug concentration; **ND** = not determined due to long half-life of nordiazepam; **$t_{max}$** = time to observed maximum plasma drug concentration.

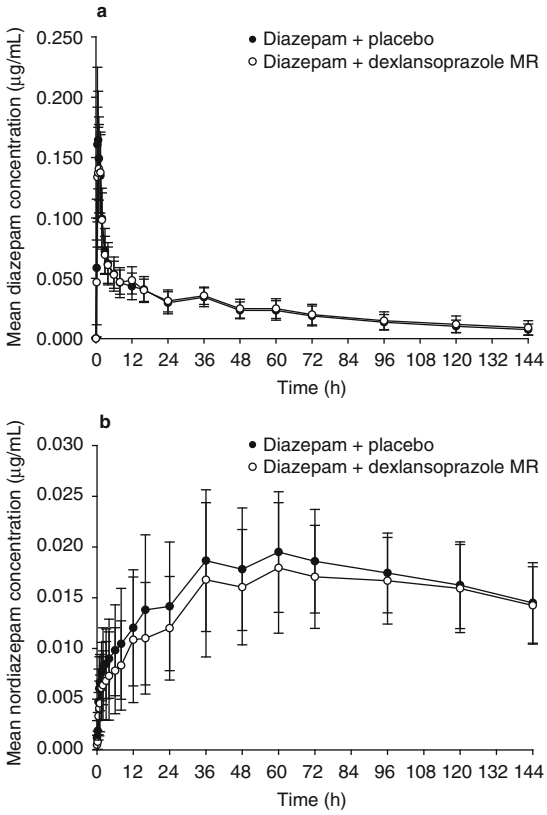


**Fig. 1.** Mean plasma concentration of diazepam (**a**) and nordiazepam (**b**) vs time profiles for diazepam coadministered with dexlansoprazole modified release (MR) [TAK-390MR] or placebo.

one of the subjects enrolled was categorized as an extensive metabolizer of CYP2C19.

#### *Pharmacokinetics*

Mean $t_{max}$, $C_{max}$ and AUC values for diazepam and nordiazepam were generally similar when diazepam was administered with either dexlansoprazole MR or placebo (table II). The mean plasma concentration-time profiles of diazepam and nordiazepam following administration of diazepam were similar for the dexlansoprazole MR and placebo regimens (figure 1a and b). The mean $t_{1/2z}$ of diazepam was slightly longer in subjects treated with dexlansoprazole MR plus diazepam (61.18 ± 33.41 hours) compared with those treated with placebo plus diazepam (51.49 ± 19.67 hours). The washout interval used appeared to be appropriate for the diazepam study since only 2 of 19 predose samples obtained in period 2 had measurable diazepam concentrations, which were 68- to 97-fold less than the observed $C_{max}$ values.

The 90% CIs for the ratios of the central values between diazepam with dexlansoprazole MR and diazepam with placebo were within the no effect range of 0.80 and 1.25 for diazepam and nordiazepam $C_{max}$ and AUC (table III), indicating that multiple oral doses of dexlansoprazole MR had no effect on the pharmacokinetics of diazepam or nordiazepam.

The estimated oral clearance in the subject taking diazepam with placebo who was genotyped as a CYP2C19 poor metabolizer appeared to be similar when the subject was taking diazepam with dexlansoprazole MR (0.81 vs 0.62 L/hour, respectively). Furthermore, the oral clearance value for diazepam in this CYP2C19 poor metabolizer was within the observed range for oral clearance values estimated for the CYP2C19 extensive metabolizer in this study. However, the effect of CYP2C19 genotype on dexlansoprazole and diazepam drug-drug interaction cannot be assessed based on data from only one CYP2C19 poor metabolizer.

#### *Safety*

Overall, 70% of subjects experienced at least one treatment-emergent adverse event. The incidence of treatment-related adverse events was slightly higher during administration of diazepam with placebo (42%) than with diazepam with dexlansoprazole MR (30%). One patient experienced a serious adverse event (perforated appendix) that led to premature discontinuation; however, the investigator did not consider this event to be related to study medication. No deaths occurred during this study. No subject had a laboratory value that was considered to be clinically significant.

### Phenytoin

#### *Baseline Demographics and Disposition of Subjects*

The effect of multiple once-daily doses of dexlansoprazole MR 90 mg on the pharmaco-

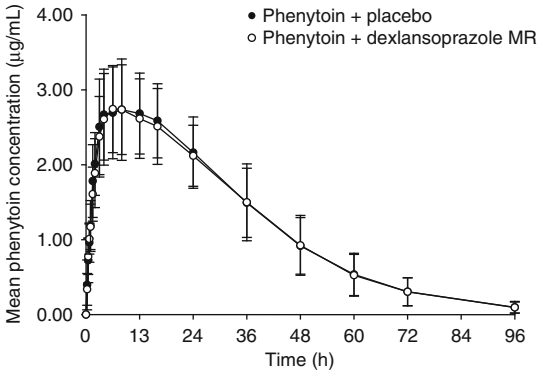


**Fig. 2.** Mean plasma concentration of phenytoin vs time profiles for phenytoin coadministered with dexlansoprazole modified release (MR) [TAK-390MR] or placebo.

kinetics of a single oral dose of phenytoin 250 mg was evaluated in 16 healthy subjects. Sixty-three percent of the subjects were White, 37% were Black, and most were men (87%). Subjects ranged in age from 20 to 35 years (mean ± SD: 25.8 ± 4.6 years at baseline). Mean height was 178.3 ± 7.7 cm, and mean weight was 80.4 ± 10.7 kg. All 16 subjects enrolled completed both regimens and were included in the pharmacokinetic and safety analyses. Genotype results were available for 15 of 16 subjects enrolled (one subject withdrew consent for genotyping). Based on CYP2C9 and CYP2C19 genotyping, all 15 subjects were phenotyped as CYP2C19 extensive metabolizers and/or CYP2C9 normal hydroxylators.

### *Pharmacokinetics*

Mean $t_{max}$, $C_{max}$ and AUC values for phenytoin were generally similar when administered with placebo or dexlansoprazole MR (table II). The mean plasma concentration-time profiles of phenytoin were nearly superimposable for phenytoin administered with dexlansoprazole MR and phenytoin administered with placebo (figure 2). The mean $t_{½Z}$ of phenytoin was also similar between the two regimens: 13.55 ± 2.46 hours for phenytoin administered with dexlansoprazole MR and 13.65 ± 2.92 hours for phenytoin administered with placebo. Since no measurable predose concentrations for phenytoin were obtained in period 2 of the phenytoin study, the selected washout interval was appropriate to evaluate the potential effect of dexlansoprazole MR on the oral bioavailability of phenytoin.

The 90% CIs for the ratios of the central values between phenytoin with dexlansoprazole MR and phenytoin with placebo were within the 'no effect' range of 0.80 to 1.25 for $C_{max}$ and AUC values, indicating that multiple oral doses of dexlansoprazole MR had no effect on the pharmacokinetics of phenytoin (table III).

### *Safety*

Overall, 50% of subjects experienced at least one treatment-emergent adverse event. The number of subjects who experienced at least one adverse event was slightly higher for the dexlansoprazole MR plus phenytoin group (31%) than for the placebo plus phenytoin group (25%). There were no deaths, serious adverse events, or withdrawals due to adverse events. No subject had a laboratory value that was considered clinically significant.

**Table III.** Bioavailability of diazepam, nordiazepam, phenytoin, theophylline, and *S*- and *R*-warfarin after coadministration of test substrates with dexlansoprazole modified release relative to that after coadministration of test substrate with placebo

| Analyte | Point estimate for $C_{max}$ ratio (90% CI) | Point estimate for $AUC_t$ ratio (90% CI) | Point estimate for $AUC_\infty$ ratio (90% CI) |
|---|---|---|---|
| Diazepam | 0.89 (0.826, 0.956) | 1.02 (0.986, 1.056) | 1.06 (1.0126, 1.119) |
| Nordiazepam | 0.95 (0.914, 0.992) | 0.93 (0.880, 0.979) | ND |
| Phenytoin | 0.97 (0.894, 1.058) | 0.98 (0.938, 1.028) | 0.98 (0.936, 1.028) |
| Theophylline | 1.05 (0.965, 1.134) | 0.96 (0.932, 0.998) | 0.96 (0.928, 0.992) |
| *S*-warfarin | 0.93 (0.840, 1.020) | 0.96 (0.933, 0.992) | 0.95 (0.923, 0.986) |
| *R*-warfarin | 0.93 (0.860, 1.003) | 0.97 (0.954, 0.994) | 0.97 (0.943, 0.992) |

**AUC** = area under the plasma concentration versus time curve; **$AUC_\infty$** = AUC from time zero to infinity; **$AUC_t$** = AUC from time zero to the time of last quantifiable sampling time point; **$C_{max}$** = observed maximum plasma drug concentration; **ND** = not determined due to long half-life of nordiazepam.

## Theophylline

### *Baseline Demographics and Disposition of Subjects*

The effect of multiple once-daily doses of dexlansoprazole MR 90 mg on the pharmacokinetics of theophylline following administration of a single intravenous infusion of aminophylline 400 mg (theophylline 315 mg) was assessed in 20 healthy subjects. All of the subjects were White, and most were women (60%). Subjects ranged in age from 23 to 55 years (mean ± SD: 36.8 ± 9.7 years at baseline). Mean height was 164.6 ± 8.1 cm, and mean weight was 72.2 ± 10.4 kg. Of the 20 subjects enrolled, 19 completed both regimens and were included in the pharmacokinetic analysis; all 20 subjects were included in the safety analysis.

### *Pharmacokinetics*

Overall, mean $t_{max}$, $C_{max}$ and AUC values for theophylline were similar when administered with placebo or dexlansoprazole MR (table II). Following administration of aminophylline, the mean plasma concentration-time profiles of theophylline were nearly superimposable for theophylline administered with dexlansoprazole MR and placebo regimens (figure 3). The mean $t_{½z}$ of theophylline was also similar in subjects who received aminophylline administered with dexlansoprazole MR compared with that obtained for aminophylline administered with placebo (8.48 ± 1.6 vs 9.26 ± 1.8 hours, respectively). Theophylline concentrations in the predose samples collected in period 2 of the study were all below the LLQ of the assay, demonstrating the adequacy of the washout period used for the theophylline-dexlansoprazole MR interaction study.

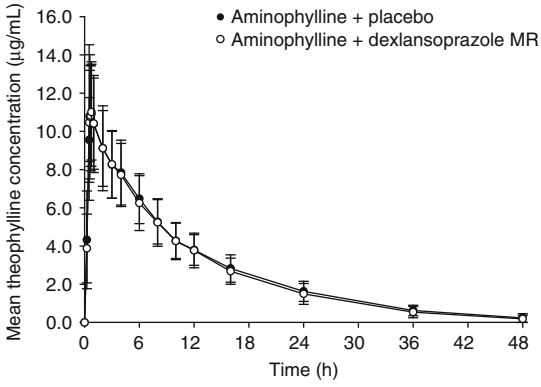


**Fig. 3.** Mean plasma concentration of theophylline vs time profiles for aminophylline coadministered with dexlansoprazole modified release (MR) [TAK-390MR] or placebo.

The 90% CIs for the ratios of the central values of theophylline $C_{max}$ and AUC values when taken with dexlansoprazole MR relative to the values when taken with placebo were within the 'no effect' range of 0.80 to 1.25, indicating that multiple oral doses of dexlansoprazole MR had no effect on the pharmacokinetics of theophylline (table III).

### *Safety*

Overall, 65% of subjects experienced at least one treatment-emergent adverse event. The percentage of subjects who experienced adverse events while receiving placebo with aminophylline was 45% compared with 25% receiving dexlansoprazole MR with aminophylline. There were no deaths, no serious adverse events, and no discontinuations due to adverse events; one subject prematurely withdrew consent. No subject had a laboratory value that was considered clinically significant.

## Warfarin

### *Baseline Demographics and Disposition of Subjects*

The effect of multiple once-daily doses of dexlansoprazole MR 90 mg on the plasma pharmacokinetics and pharmacodynamics of a single oral dose of warfarin 25 mg was explored in 19 healthy subjects. Forty-seven percent of subjects were White, 26% were Black, and all were men. Subjects ranged in age from 18 to 48 years (mean ± SD: 33.7 ± 9.3 years at baseline). Mean height was 179.4 ± 7.5 cm, and mean weight was 83.3 ± 10.1 kg. Based on CYP2C9 genotyping, 17 subjects were categorized as CYP2C9 normal hydroxylators and two as CYP2C9 reduced hydroxylators.

### *Pharmacokinetics*

Mean $t_{max}$, $C_{max}$ and $AUC_{\infty}$ values for *S*-warfarin and *R*-warfarin were generally similar when warfarin was administered with dexlansoprazole MR or with placebo (table II). The mean plasma concentra-

tion-time profiles for *S*-warfarin and *R*-warfarin were nearly superimposable for warfarin administered with dexlansoprazole MR or placebo regimens (figure 4). The mean $t_{½z}$ values ± SD for *S*-warfarin were similar between the two regimens: 42 ± 9 hours for warfarin with dexlansoprazole MR and 40 ± 7 hours for warfarin with placebo. The estimated mean $t_{½z}$ values for *R*-warfarin were approximately the same (49 ± 11 hours) for warfarin with dexlansoprazole MR and warfarin with placebo regimens. The washout interval used in the warfarin-dexlansoprazole MR study was adequate to evaluate the potential effect of dexlansoprazole MR on the oral bioavailability of *R*- and *S*-warfarin. *R*- or *S*-warfarin concentrations were at least 51- and 32-fold lower, respectively, than the observed $C_{max}$ values in 13 of 18 predose samples obtained in peroid 2.

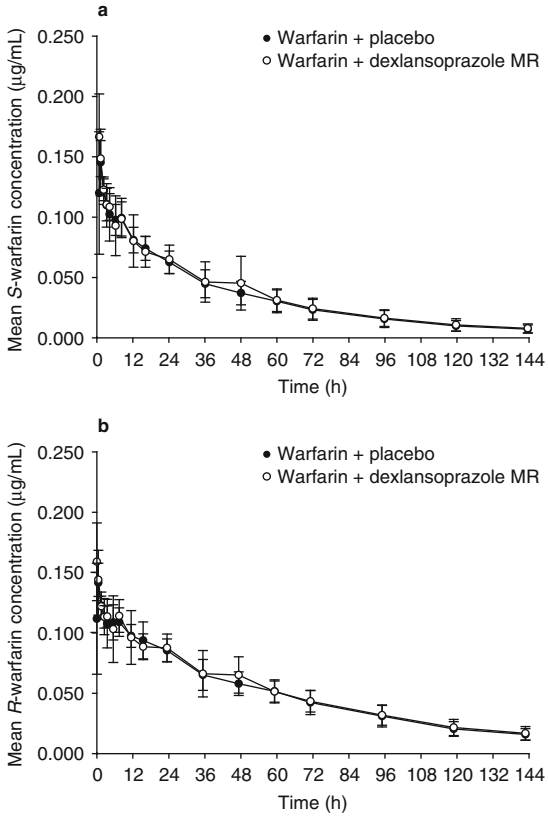


**Fig. 4.** Mean plasma warfarin concentration vs time profiles of *S*-warfarin (**a**) and *R*-warfarin (**b**) following coadministration of warfarin with dexlansoprazole modified release (MR) [TAK-390MR] or placebo.

The differences for the estimated central values for $C_{max}$ and $AUC_{\infty}$ values for S-warfarin and R-warfarin when warfarin was administered with dexlansoprazole MR relative to when warfarin was administered with placebo were ≤7%. In addition, the 90% CIs for the ratios of the central values for *S*-warfarin and *R*-warfarin $C_{max}$ and AUC when warfarin was administered with dexlansoprazole MR relative to when warfarin was administered with placebo were within the 'no effect' range of 0.80 to 1.25, indicating that multiple daily doses of dexlansoprazole MR had no effect on the pharmacokinetics of *S*-warfarin or *R*-warfarin (table III).

Of the two subjects who were found to be CYP2C9-reduced hydroxylators, one was prematurely discontinued from the study because of a failed drug screen. Therefore, it was not possible to compare the effect of genotype on the systemic exposure of warfarin in this study. The estimated oral clearance value for *S*-warfarin in the CYP2C9-reduced hydroxylator (~300 mL/hour) who completed the study was lower than that estimated for the rest of the subjects who were normal CYP2C9 hydroxylators (344–766 mL/hour). However, oral clearance of *S*-warfarin in this reduced hydroxylator appeared to be similar following administration of warfarin with dexlansoprazole MR 90 mg (300 mL/hour) or placebo (321 mL/hour). Again, the effect of CYP2C19 genotype on dexlansoprazole and warfarin drug-drug interaction cannot be assessed based on data from only one CYP2C9 reduced hydroxylator.

### *Pharmacodynamics*

The mean INR time curves (over 144 hours postdose) were nearly superimposable regardless of whether warfarin was coadministered with placebo or dexlansoprazole MR (figure 5). The differences in mean $INR_{144}$ and $INR_{max}$ between the two regimens were neither statistically significant ($p > 0.05$) nor clinically significant, indicating that dexlansoprazole had no effect on the anticoagulant activity of a single 25 mg dose of warfarin.

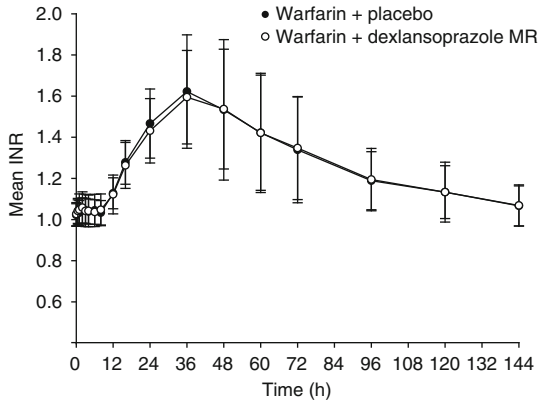


**Fig. 5.** Mean international normalized ratio (INR) vs time profiles for warfarin following coadministration of warfarin with dexlansoprazole modified release (MR) [TAK-390MR] or placebo.

#### *Safety*

Five of 19 subjects (26%) reported at least one treatment-emergent adverse event: two (11%) when receiving warfarin with dexlansoprazole MR and three (17%) when receiving warfarin with placebo. All adverse events were mild, and no subject experienced a treatment-related adverse event during the study. With the exception of the anticipated pharmacological effect on prothrombin times, the magnitudes of the mean changes from baseline in laboratory values during each of the dosage regimens were small and generally unremarkable. No subject had a laboratory value that was considered clinically important. Coadministration of warfarin with dexlansoprazole MR was generally well tolerated.

#### *Sequence/Period Effect*

Period and sequence effects were tested in all ANOVA models. The sequence effect was not statistically significant in any of the four studies. Period effect was statistically significant in the diazepam interaction study for $\ln(C_{max})$ of diazepam and nordiazepam, and for $\ln(AUC_t)$ of nordiazepam. Period effect was also observed in the warfarin interaction study for the pharmacodynamic parameters $INR_{max}$ and $INR_{144}$. The factor of period in the ANOVA accounted for the differences between periods. Because only subjects with parameter estimates for both periods were included in the models, the period effect on each of the regimens was considered to be balanced. Consequently, the existence of the period effect did not affect the comparison of two regimens in each study, but rather confirmed the appropriateness of the crossover design.

## Discussion

Drug interactions are a common cause of adverse events.[37] Although generally considered safe, PPIs are widely prescribed and have the potential to interact with other medications that share the CYP metabolic pathways. A large retrospective claims study of approximately 67 000 patients from 23 US managed-care plans showed that 58% of patients treated with PPIs were also taking drugs with the potential to interact with PPIs.[13] This finding, in conjunction with the broad-based use of PPIs in diverse populations, underscores the importance of characterizing the interaction potential of existing and emerging PPIs.

The potential for drug interactions with other PPIs has been demonstrated in numerous studies. It has been recommended that patients taking either diazepam or phenytoin in combination with omeprazole should be closely monitored.[2,4] Both omeprazole and esomeprazole have been shown to decrease the clearance and prolong the half-life of diazepam in healthy subjects.[8-10,26] In the current evaluation of diazepam coadministered with dexlansoprazole MR in healthy subjects, dexlansoprazole MR had no statistically significant impact on the mean $t_{1/2z}$ of diazepam and, based on bioavailability, it is concluded that dexlansoprazole MR has no effect on the pharmacokinetics of diazepam or nordiazepam. Since quantitation of plasma nordiazepam provides a direct assessment of the effect of dexlansoprazole on the *in vivo* activity of CYP2C19, it is unlikely that dexlansoprazole MR will affect the metabolism of other drugs metabolized by this isoenzyme.

Omeprazole has also been shown to increase the AUC of phenytoin and reduce its plasma clearance, probably as a result of competitive CYP2C19 inhibition.[10,34] In the current investigation of the effect of dexlansoprazole MR on the pharmacokinetics of phenytoin, mean $t_{max}$, $C_{max}$, AUC and $t_{1/2z}$ values

were generally similar when phenytoin was administered with dexlansoprazole MR or placebo. The results of this study suggest that dexlansoprazole MR does not significantly affect hepatic CYP2C19 or CYP2C9 activities and that dexlansoprazole MR can likely be administered with drugs that are metabolized by these enzymes.

Omeprazole and lansoprazole have also been shown *in vitro* to be potential inducers of hepatic CYP1A2, which is involved in the metabolism of theophylline.[23] In addition, *in vivo*, lansoprazole has been shown to cause a minor increase (13%) in theophylline systemic clearance with a corresponding decrease in its AUC, although these changes in theophylline pharmacokinetics were deemed not likely to be clinically important.[24] Nevertheless, the labelling for lansoprazole notes that theophylline may require additional dose titration to ensure clinically effective blood levels in patients starting or stopping lansoprazole therapy.[16] In the current evaluation of multiple once-daily doses of dexlansoprazole MR with aminophylline in healthy subjects, the mean $t_{max}$, $C_{max}$, AUCs and $t_{½Z}$ values for theophylline were similar when aminophylline was administered with dexlansoprazole MR or placebo. Dexlansoprazole MR did not appear to alter the *in vivo* activity of CYP1A2 in humans and, therefore, is not likely to alter the metabolism of other drugs metabolized by this enzyme. No dosage adjustment for theophylline is required when given concomitantly with dexlansoprazole MR.

Product labels for all six marketed PPIs – omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole and omeprazole/sodium bicarbonate – state that there have been reports of increased prothrombin time in patients taking PPIs with warfarin. Furthermore, it is recommended that patients receiving concomitant therapy with these PPIs and warfarin be monitored for increases in INR and prothrombin time.[11,16-20] Separate studies of omeprazole and esomeprazole, in healthy subjects and in patients anticoagulated with warfarin, have indicated the potential for both drugs to interact with CYP2C19, which is one of the CYP isoenzymes responsible for metabolism of warfarin.[38-40] Both omeprazole and esomeprazole have shown modest changes in the pharmacokinetics of *R*-warfarin (the less pharmacologically potent enantiomer), although these changes were deemed unlikely to have safety consequences. In the current study, dexlansoprazole MR had no effect on the pharmacokinetics or pharmacodynamics of single high dose of warfarin in healthy subjects. This finding is particularly important since warfarin has a very narrow therapeutic range and is widely used in patients with multiple co-morbid conditions receiving polypharmacy.

Administration of dexlansoprazole MR with diazepam, phenytoin, theophylline (administered as intravenous aminophylline) or warfarin was well tolerated in these trials in a total of 75 healthy subjects. No safety concerns were associated with use of dexlansoprazole MR alone or in combination with any of the study drugs.

## Conclusion

Concomitant administration of dexlansoprazole MR with diazepam, phenytoin, warfarin or theophylline (administered as intravenous aminophylline) does not affect the single-dose pharmacokinetics of these coadministered drugs, and therefore it is unlikely that dexlansoprazole MR will alter the pharmacokinetic profile of other drugs metabolized by CYP2C19, CYP2C9, CYP1A2 and perhaps CYP3A. In addition, dexlansoprazole MR coadministered with warfarin did not affect the anticoagulant activity of warfarin. This favourable drug interaction profile of dexlansoprazole MR may provide benefits for patients who require PPI therapy in conjunction with other medications.

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Correspondence: Dr *Majid Vakily*, Clinical Pharmacology, Takeda Global Research and Development Center, Inc., 675 North Field Drive, Lake Forest, IL 60045, USA.
E-mail: majid.vakilynejad@tgrd.com