ORIGINAL RESEARCH ARTICLE

Clin Drug Investig 2012; 32 (5): 319-332
1173-2563/12/0005-0319/$49.95/0

Absorption, Distribution, Metabolism and Excretion of [^{14}C]Dexlansoprazole in Healthy Male Subjects

Brian Grabowski and *Ronald D. Lee*

Takeda Global Research & Development Center, Inc., Deerfield, IL, USA

Abstract

Background and Objective: The proton pump inhibitor dexlansoprazole is a modified-release formulation of dexlansoprazole, an enantiomer of lansoprazole, which employs a Dual Delayed Release™ (DDR) delivery system. This study was conducted in healthy subjects to assess the absorption, distribution, metabolism and excretion of a 60 mg dose of [^{14}C]dexlansoprazole.

Methods: After multiple daily doses of dexlansoprazole DDR for 4 days followed by a single dose of [^{14}C]dexlansoprazole on day 5, absorption, distribution, metabolism and elimination of [^{14}C]dexlansoprazole were assessed in six healthy male subjects whose CYP (cytochrome P450) 2C19 metabolizer status was also determined.

Results: Five subjects were phenotyped as extensive metabolizers (EMs) and one subject was a poor metabolizer (PM). Recovery of radioactivity in urine and faeces averaged 98% after 7 days (51% in urine and 48% in faeces) post-^{14}C dosing. In plasma, dexlansoprazole was the largest component detected, with the main metabolites in the EM subjects being 5-glucuronyloxy dexlansoprazole and 5-hydroxy dexlansoprazole (CYP2C19 mediated), whereas the PM subject had greater amounts of dexlansoprazole sulfone (CYP3A mediated). Dexlansoprazole was not detected in urine; six metabolites were identified accounting for an average of 86% of the urinary radioactivity, with 5-glucuronyloxy dexlansoprazole, 5-glucuronyloxy dexlansoprazole sulfide, 2-S-*N*-acetylcysteinyl benzimidazole and 5-sulfonyloxy dexlansoprazole sulfide being the primary metabolites. In faeces, parent drug and six identified metabolites accounted for 23% and 72%, respectively, of the faecal radioactivity, with 5-hydroxy dexlansoprazole sulfide and dexlansoprazole sulfide being predominant.

Conclusion: Overall, the results indicate that [^{14}C]dexlansoprazole was well absorbed and extensively metabolized by oxidation, reduction and conjugation to 13 identified metabolites.

Introduction

Dexlansoprazole Dual Delayed Release™ (DDR) capsule is a proton pump inhibitor (PPI) approved in adults for the treatment of symptomatic non-erosive gastro-oesophageal reflux disease, healing of erosive oesophagitis (EO) and maintenance of healed EO.[1] Dexlansoprazole is acid labile and requires protection in the lower pH environment of the stomach. Dexlansoprazole DDR is a modified-release formulation of dexlansoprazole that employs an innovative delivery system with DDR technology. The formulation is designed to deliver the drug in two discrete phases of release by the use of two types of enteric-coated granules, each providing a different pH-dependent dissolution profile.[2] The first plasma peak is designed to be attained approximately 1–2 hours post-dose and the second plasma peak approximately 4–5 hours after dosing.[3]

Doses of 30, 60, 90 and 120 mg of dexlansoprazole DDR have been evaluated clinically and are generally dose-proportional with regard to maximum plasma drug concentration (C_{max}) and area under the plasma concentration-time curve (AUC).[2] The apparent half-life ($t_{½}$) of dexlansoprazole typically ranged from 1 to 2 hours, regardless of the dose, and no appreciable accumulation of dexlansoprazole was observed following once-daily dosing. In addition, the pharmacokinetics of dexlansoprazole were shown to be time-independent based on the similar systemic exposure after single or multiple doses. Gastric pH is generally 1–2, and after multiple daily doses of dexlansoprazole DDR gastric pH is typically >4.[2] Dexlansoprazole is extensively bound to human plasma proteins (~97%).[1] The metabolism of most PPIs involves primarily cytochrome P450 (CYP) isoenzymes 3A4 and 2C19.[4] Similar to other PPIs, the major route of metabolism of dexlansoprazole is the hydroxylation of the benzimidazole ring at the 5-position, which was demonstrated in preclinical studies in rats and dogs[5,6] and is facilitated by CYP2C19 in humans. CYP2C19 isoenzyme activity varies, with approximately 2–4%, 13–25% and 1–5% of the White, Asian and Black populations, respectively, considered poor metabolizers (PMs).[7] The impact of CYP2C19 phenotypes (extensive vs PMs) on PPI pharmacokinetics, pharmacodynamics and efficacy has been well characterized.[8-10]

This study was conducted in healthy subjects to assess the absorption, distribution, metabolism and excretion (ADME) after administration of a 60 mg oral dose of carbon-14 labelled [^{14}C]dexlansoprazole. Radiolabelled clinical ADME studies generally involve small numbers of subjects, and are required for all regulatory submissions of new chemical entities. The administered radiolabelled dexlansoprazole allows for the determination of recovery of total drug-related substances in urine and faeces (mass balance), and for the identification of metabolites in various matrices. We also examined the impact of CYP2C19 metabolizer status on the ADME of dexlansoprazole.

Subjects and Methods

Subject Selection and Ethical Considerations

Six male subjects between the ages of 18 and 55 years with body mass indices of no more than 30 kg/m^2 participated in the study. Subjects were to be in good health, as evidenced by medical history, physical examination, electrocardiogram (ECG) and laboratory profiles.

The study protocol and the informed consent forms were reviewed and approved by the Covance Clinical Research Unit Institutional Review Board (Madison, WI, USA). Study participants provided written informed consent prior to study entry. The study was conducted in accordance with the US FDA's Good Clinical Practice Guidelines, all applicable local regulations, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), and the Declaration of Helsinki.

Study Design and Drug Administration

This was a phase I, single-centre (Covance Clinical Research Unit, Inc), open-label study conducted in six healthy male volunteers to investigate the ADME of dexlansoprazole. The CYP2C19 metabolizer status of each subject was assessed by determining the *CYP2C19* genotype on day –1. Since dexlansoprazole is acid labile, all subjects

received a daily single 60 mg oral dose of non-radiolabelled dexlansoprazole DDR (Takeda Pharmaceutical Company, Ltd, Osaka, Japan) in order to increase intragastric pH. A standardized breakfast was served 1 hour after dexlansoprazole DDR dose administration on days 1 through 4. Breakfast was not served on day 5. One hour prior to dose administration on day 5, individual dose vials containing 60 mg of radiolabelled [14C]dexlansoprazole were formulated as oral preparations in 10 mL of Maalox® (aluminium hydroxide and magnesium hydroxide) suspension to provide additional gastric pH protection.[11] The preparations were well mixed and, under supervision, each subject self-administered the liquid preparation. After administration, all dose vials were tested for residual radioactivity to determine the absolute amount of radioactivity administered. Following dosing of [14C]dexlansoprazole, blood, urine and faecal samples were collected from day 5 to day 12 to measure the concentration of dexlansoprazole and its metabolites, and to determine the total radioactivity and metabolic profile of select samples containing sufficient radioactivity.

Subjects were discharged when: radioactivity levels in blood and plasma contained less than three times the background radioactivity, either two consecutive samples of both urine and faeces contained less than 1% of administered radioactivity or ≥90% of the radioactive dose could be accounted for in the urine and faeces.

Materials

[14C]Dexlansoprazole was used as a tracer in order to evaluate mass balance and profile the metabolites in various matrices. Data in Sprague Dawley and Long-Evans rats[12] indicated that whole body radiation exposure in a 70 kg man following a single 100 μCi dose of [14C]dexlansoprazole was calculated to be 11.2 mrem, well below the FDA exposure limit of 3000 mrem for a single dose in humans. Following administration of [14C]dexlansoprazole in rats, five tissues with the highest exposure of radiation were the blood, stomach (gastric mucosa), liver, eye and uveal tract. Estimated exposures in these corresponding tissues in humans were approximately 7, 8, 8, 9 and 123 mRad or mrem, respectively, at the expected target dose of 100 μCi. These values are well below the allowable exposure limit of 3000 mrem in humans.[12]

[14C]Dexlansoprazole was labelled at the 2-carbon position on the benzimidazole ring (99% purity). The radiolabelled compound was purified and blended with non-radiolabelled dexlansoprazole active pharmaceutical ingredient (Takeda Pharmaceutical Company, Ltd) to a specific activity of 1.7 μCi/mg under current Good Manufacturing Process by Aptuit, Inc. (Lenexa, KS, USA), and sent to the clinical site as a powder in preweighed individual dose vials, each containing approximately 60 mg (100 μCi) of dexlansoprazole. A 60 mg dose of dexlansoprazole was chosen as it was the highest clinical dose and it afforded sufficient mass for metabolite identification work.

Reference standards were synthesized and supplied by Takeda Pharmaceutical Company, Ltd. For identification of metabolites by high-performance liquid chromatography (HPLC) and liquid chromatography tandem mass spectrometry (LC-MS/MS), the following reference standards were used: dexlansoprazole and metabolites 5-hydroxy dexlansoprazole; dexlansoprazole sulfone; 5-hydroxy dexlansoprazole sulfone; dexlansoprazole sulfide; 5-hydroxy dexlansoprazole sulfide; 4-hydroxy dexlansoprazole sulfide; and 2-*S*-*N*-acetylcysteinyl benzimidazole. Internal standards dexlansoprazole-d_4, 5-hydroxy dexlansoprazole-d_4 and dexlansoprazole sulfone-d_4 were synthesized and supplied by Takeda Pharmaceutical Company, Ltd, and used for quantitation by LC-MS/MS.

Sampling Times

Venous blood samples (2 × 10 mL) were collected in tubes containing heparin. Predose (0-hour) samples were obtained approximately 30 minutes before dosing with dexlansoprazole DDR 60 mg on day 1 and [14C]dexlansoprazole in Maalox® on day 5. In addition, venous blood samples were collected at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, 16, 24, 36, 48, 72, 96, 120, 144 and 168 hours after dosing on day 5. On day 1, urine was collected predose and on day 5 from 0 to 4, 4 to 8, 8 to 12 and 12 to

24 hours post-dose and, if necessary, pooled into a composite sample for each collection interval. Thereafter, urine was pooled into 24-hour composite samples for each subsequent day of the study for up to 7 days post-radioactive dosing. Weight and pH were obtained for each urine pool and the pH was adjusted to approximately 9.5 with 1 N sodium hydroxide to ensure stability of dexlansoprazole. Faecal samples were collected as excreted at predose on day 1, and at 0–12 and 12–24 hours post-dose on day 5. Thereafter, faecal samples were pooled into 24-hour composite samples for up to 7 days post-radioactive dosing.

CYP2C19 Genotyping

The CYP2C19 metabolizer status of each subject was assessed by determining the *CYP2C19* genotype (homozygous or heterozygous for alleles *wt*, **2, *3, *4* or **5;* Cogenics, Inc., Morrisville, NC, USA). On day −1 of dosing, a single 10 mL blood sample was collected from each subject into an EDTA Vacutainer tube and stored at −20°C before DNA extraction. DNA from whole blood samples was isolated and purified using the Gentra Puregene DNA Isolation Kit™ (Qiagen, Inc., Valencia, CA, USA). DNA samples were aliquoted, then digested with the restriction endonucleases *SmaI*, *BamHI*, *PstI* or *BstXI*, individually, per manufacturer instructions, for identification of alleles *wt*, **2, *3, *4* and **5,* respectively. *CYP2C19* genotypes were determined by electrophoretically generated patterns of restriction fragment length polymorphisms specific to each allele and genotype.

Quantitation of Dexlansoprazole, 5-Hydroxy Dexlansoprazole and Dexlansoprazole Sulfone

Concentrations of dexlansoprazole, 5-hydroxy dexlansoprazole and dexlansoprazole sulfone in plasma were determined using a validated LC-MS/MS method (MDS Pharma Services, Lincoln, NE, USA). Plasma samples (0.1 mL) were spiked with deuterated internal standards dexlansoprazole-d_4, 5-hydroxy dexlansoprazole-d_4 and dexlansoprazole sulfone-d_4, and extracted using a liquid-liquid extraction procedure with methyl-*tert*-butyl ether.

Total Radioactivity Analyses

Duplicate 0.2 mL aliquots of plasma and urine were assayed for total radioactivity directly in Ultima Gold™ XR scintillation fluid by counting for at least 5 minutes or 100 000 dpm on a Packard TriCarb® 2900TR. Duplicate 0.2 g aliquots of whole blood were oxidized in a Packard Sample Oxidizer Model 307 (Packard Instruments, Meriden, CT, USA) using a mixture of Permafluor® and Carbo-Sorb®. Faecal samples were homogenized with a 50% methanol solution using probe-type homogenizer. Duplicate 0.2 g aliquots of faecal homogenate were oxidized in a Packard Sample Oxidizer Model 307 using a mixture of Permafluor® and Carbo-Sorb®. Radioactivity was quantified using a Packard TriCarb® 2900TR liquid scintillation counter. For total radioactivity determinations, all samples were analysed with automatic quench correction using an external standard method.

Residual radioactivity in each subject's dose vial after administration of [^{14}C]dexlansoprazole was determined by addition of a 50% methanol solution and allowing the vials to extract overnight. Duplicate 0.5 g aliquots were assayed for total radioactivity directly in Ultima Gold™ XR scintillation fluid on a Packard TriCarb® 2900TR.

The total radioactivity associated with each individual's red blood cells was calculated using the following equation:

$$\text{Radioactivity/g red blood cells} = \frac{(\text{dpm/g whole blood}) - (\text{dpm/g plasma} \times [1 - \text{haematocrit}])}{\text{haematocrit}} \quad \text{(Eq. 1)}$$

Metabolic Profiling

Plasma samples up to 16 hours post-dose, urine collected from 0 to 4, 4 to 8, 8 to 12 and 12 to 24 hours post-dose, and faecal collections from the various intervals up to 96 hours post-dose from each subject were used for metabolic profiling. Total radioactivity measurements and metabolic profiling were performed by Covance Laboratories, Inc.

All HPLC instrument and chromatographic conditions used for mass spectrometric characterization were the same as those used for me-

tabolic profiling. Select plasma, urine and faecal samples were analysed by HPLC and full-scan mass spectroscopy in the positive ion mode in order to obtain a protonated molecular ion in the chromatographic region associated with a radioactive peak. Based on the fragmentation of each metabolite reference standard, multiple reaction monitoring was also conducted for each of the selected plasma, urine and faecal samples to determine metabolite composition. For those radioactive peaks where the retention time did not match a potential metabolite reference standard, analysis by collision-induced dissociated LC-MS/MS was performed based on the respective protonated molecular ion to obtain structural fragmentation data.

Pharmacokinetic Analyses and Statistical Methods

Pharmacokinetic parameters for total radioactivity, dexlansoprazole, 5-hydroxy dexlansoprazole and dexlansoprazole sulfone in plasma were estimated using standard non-compartmental methods with WinNonlin Professional Version 4.1 (Pharsight Co, Mountain View, CA, USA). Concentrations less than the lower level of quantitation were reported as zero and included as zero in the descriptive statistics. All pharmacokinetic calculations were performed prior to rounding.

The observed C_{max} for total radioactivity, dexlansoprazole, 5-hydroxy dexlansoprazole and dexlansoprazole sulfone in plasma and the time to maximum (peak) drug concentration (t_{max}) were obtained directly from the concentration-time profile for each subject. The apparent terminal elimination-rate constant (λ_z) was estimated using least squares regression analysis of the terminal log-linear portion of the concentration-time profiles. Apparent terminal elimination-phase half-life ($t_{½z}$) was calculated as $\ln(2)/\lambda_z$. AUC from time zero to the last quantifiable concentration (AUC_{last}) was calculated by the log-linear trapezoidal rule. AUC from time zero to 24 hours (AUC_{24}) was estimated using partial areas computation, and in some cases extrapolation to 24 hours using the following formula when the last quantifiable concentration (C_{last}) occurred before 24 hours:

$$AUC_{24} = AUC_{last} + C_{last}/\lambda_z\left(1 - e^{\lambda_z(24 - t_{last})}\right) \quad \text{(Eq. 2)}$$

The plasma ratios of AUC_{24} for 5-hydroxy dexlansoprazole and dexlansoprazole sulfone metabolites to AUC_{24} for parent drug were also calculated. For dexlansoprazole plasma concentrations only, oral clearance (CL/F) was estimated by dividing dose by AUC_{24}, and apparent volume of distribution during the terminal phase (V_z/F) was estimated as CL/λ_z.

Plasma concentrations of dexlansoprazole and its metabolites, total radioactivity results and derived pharmacokinetic parameters were tabulated and descriptive statistics were computed. Urine and faecal total radioactivities, expressed as a percentage of the total dose, were tabulated and descriptive statistics were computed.

Safety Assessments

Safety variables included adverse events (AEs), clinical laboratory tests (haematology, serum chemistry and urinalysis), vital signs, physical examination and ECG results. An AE was any untoward medical occurrence in a subject, representing a change from baseline, and thus could have been any new or worsened unintended sign, symptom, disease or abnormal laboratory finding. AEs were rated as mild (transient and easily tolerated), moderate (caused discomfort and interrupted usual activities) or severe (caused considerable interference with usual activities and may have been incapacitating or life threatening). Relationship to study drug was judged as definite, probable, possible or not related. AEs were collected from the time the subject signed the informed consent form until 30 days after study drug was discontinued.

Results

Six healthy male subjects participating in this study had a mean ± SD age of 26.0 ± 6.99 years and body weight of 77.8 ± 7.47 kg. Five subjects were White and one was Black. The administered doses contained 58.2–59.1 mg (99.0–100 μCi) of

[^{14}C]dexlansoprazole, with a mean of 58.8 mg (99.8 μCi) as corrected for residual radioactivity remaining in the vials after dosing.

Genotyping

Based on genotyping results of *CYP2C19* alleles, four subjects were homozygous wild type/wild type (*wt*/*wt*), one subject was heterozygous (**2*/*wt*), and one subject was homozygous (**2*/**2*). Thus, the inferred phenotypes of five subjects (*wt*/*wt* and **2*/*wt*) were categorized as CYP2C19 extensive metabolizers (EMs), which represents normal metabolic capacity, and one subject (**2*/**2*) was designated a CYP2C19 PM.

Recovery in Urine and Faeces (Mass Balance)

By 168 hours post-dose, all subjects had achieved exit criteria. Cumulative recovery of total radioactivity in urine and faeces from all six subjects averaged 98.28 ± 4.0% (mean ± SD) over 168 hours post-dose. Radioactivity in urine and faeces was nearly evenly distributed, with an overall mean recovery of 50.69 ± 9.0% in urine and 47.59 ± 7.3% in faeces (figure 1). The majority of the radioactivity was recovered in the urine (approximately 46% of the dose) within 48 hours and in the faeces (approximately 45% of the dose) within 96 hours. Thereafter, an average of less than 2% of the dose in urine or faeces was excreted in any subsequent 24-hour interval.

Pharmacokinetics of Total Radioactivity and Dexlansoprazole, 5-Hydroxy Dexlansoprazole and Dexlansoprazole Sulfone in Plasma and Radioactivity Associated with Red Blood Cells

Following multiple daily 60 mg doses of dexlansoprazole DDR for 4 days and a single 60 mg dose of [^{14}C]dexlansoprazole on day 5, plasma concentration-time profiles of total radioactivity and dexlansoprazole are shown in figure 2. Plasma concentrations of 5-hydroxy dexlansoprazole and dexlansoprazole sulfone are shown in figure 3.

Plasma concentrations of total radioactivity, dexlansoprazole, 5-hydroxy dexlansoprazole and dexlansoprazole sulfone were quantifiable at the first sampling time-point (0.25 hours post-dose) for all subjects with the exception of 5-hydroxy dexlansoprazole in the PM subject, which was below the quantifiable limit until the 0.5-hour

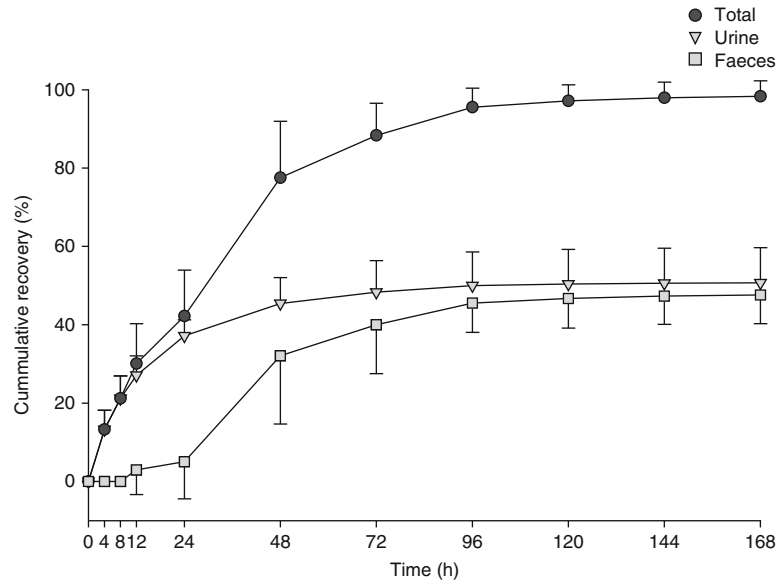

Fig. 1. Mean (SD) cumulative recovery of total radioactivity in urine and faeces (n = 6) following 60 mg doses of dexlansoprazole DDR for 4 days and a single 60 mg dose of [^{14}C]dexlansoprazole on day 5. **DDR** = Dual Delayed Release™.

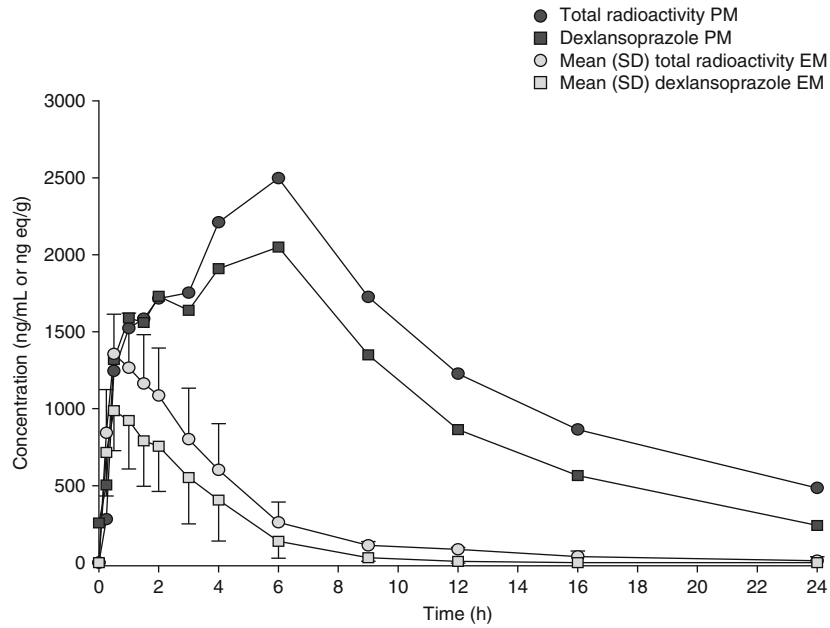

Fig. 2. Plasma concentration-time profiles of total radioactivity and dexlansoprazole in extensive metabolizer (EM) and poor metabolizer (PM) subjects on day 5 following 60 mg doses of dexlansoprazole DDR for 4 days and a single 60 mg dose of [^{14}C]Dexlansoprazole on day 5. **DDR** = Dual Delayed Release™; **SD** = standard deviation.

sample. The last quantifiable plasma concentrations (C_{last}) of dexlansoprazole were at 9–12 hours in the EM subjects and at 48 hours for the PM subject. Calculated concentrations of radioactivity in red blood cells were minimal and ranged from a mean of 0.00 to 81.1 ng eq/g over 12 hours, whereas concentrations of radioactivity in plasma were much greater and ranged from a mean of 277 to 1340 ng eq/g over 12 hours.

Pharmacokinetic parameter estimates of total radioactivity, dexlansoprazole, 5-hydroxy dexlansoprazole and dexlansoprazole sulfone in plasma are shown in table I. In EM subjects, peak plasma concentrations were attained within approximately 0.60 hours for total radioactivity, dexlansoprazole and its two metabolites. Additionally, the AUC_{24} for dexlansoprazole and its two metabolites accounted for approximately 64% of the circulating radioactivity when compared with the AUC_{24} for total radioactivity. A similar comparison in the PM subject demonstrated that approximately 96% of the plasma radioactivity was associated with dexlansoprazole and its two metabolites. Mean metabolite-to-parent drug AUC_{24} ratios for 5-hydroxy dexlansoprazole and dexlansoprazole sulfone were 8.8% and 0.6%, respectively, for the EM subjects and 0.1% and 22.2%, respectively, for the PM subject. Metabolizer status appeared to have a great influence on the $t_{½}$ of dexlansoprazole and 5-hydroxy dexlansoprazole, as the respective harmonic mean values for these analytes for the PM subject were approximately four times and three times greater compared with those mean $t_{½}$ values for the EM subjects. Additionally, mean dexlansoprazole oral clearance and apparent volume of distribution values in the EM subjects were approximately nine times and two times greater, respectively, compared with those for the PM subject. This loss of CYP2C19 activity can also be clearly seen with the 5-hydroxy dexlansoprazole-to-parent drug AUC ratios, where this ratio for the CYP2C19-dependent formation of 5-hydroxy dexlansoprazole in the PM subject was approximately 1% that of the EM subjects. Conversely, dexlansoprazole sulfone-to-dexlansoprazole AUC ratio was approximately

37 times that for the PM subject when compared with the EM subjects, indicating alternate pathways of metabolism of parent drug for the PM subject.

Metabolite Profiling and Identification

Overall, at least 19 radioactive peaks were detected in plasma, urine and faeces combined, with up to ten metabolites detected in plasma, 16 in urine and up to seven in faeces. Identification of dexlansoprazole metabolites was determined primarily by comparing retention times and mass spectra data of metabolite reference standards with those radioactive peaks. Where reference standards were not available, tentative structures were assigned based on molecular ion and mass spectrometric fragmentation data.

Plasma profiles of [^{14}C]dexlansoprazole and its metabolites were determined from 0.25-, 0.5-, 1-, 1.5-, 2-, 3-, 4- and 6-hour plasma samples collected from each subject, and a 16-hour sample collected from the PM subject. Parent drug and its metabolites in the plasma radiochromatograms were quantitated and are listed in table II. Although up to ten metabolites were detected in plasma, 5-glucuronyloxy dexlansoprazole, 5-glucuronyloxy dexlansoprazole sulfide and 5-hydroxy dexlansoprazole were the primary metabolites detected in the EM subjects. In contrast, dexlansoprazole sulfone was the primary metabolite detected in the PM subject, with dexlansoprazole sulfide present in lesser quantities.

Metabolic profiling of urine from each subject was determined up to 24 hours post-dose, and is summarized in table III. While parent drug was not detected in urine, an average of up to 86% of the radioactivity excreted in urine was tentatively identified. In the EM subjects, 5-glucuronyloxy dexlansoprazole and 5-glucuronyloxy dexlansoprazole sulfide were the major metabolites observed, while 2-S-*N*-acetylcysteinyl benzimidazole was the major metabolite detected in the PM subject. From all subjects, other urinary metabolites identified were 2-S-*N*-acetylcysteinyl hydroxybenzimidazole, 5-sulfonyloxy dexlansoprazole sulfide and 4-sulfonyloxy dexlansoprazole, together with other unknown metabolites each accounting for ≤3% of

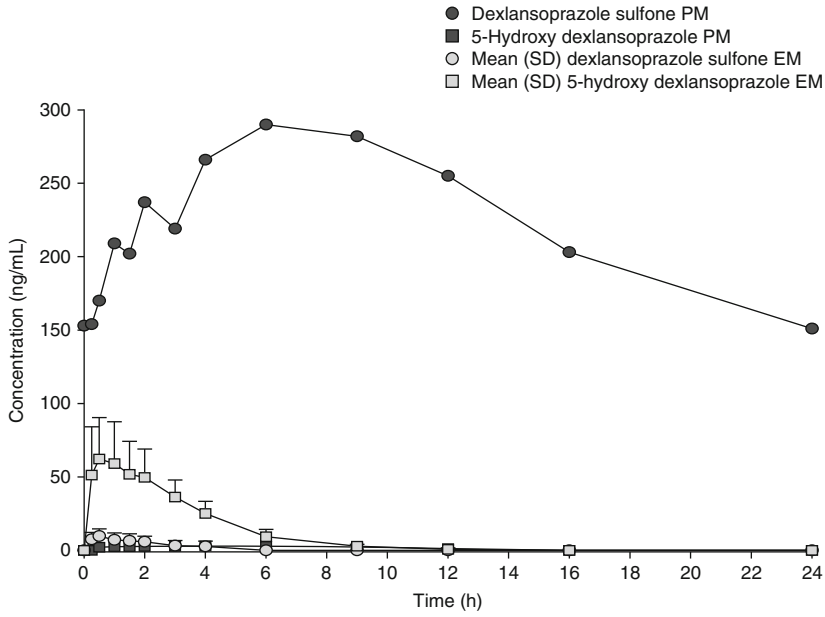

Fig. 3. Plasma concentration-time profiles of 5-hydroxy dexlansoprazole and dexlansoprazole sulfone in extensive metabolizer (EM) and poor metabolizer (PM) subjects on day 5 following 60 mg doses of dexlansoprazole DDR for 4 days and a single 60 mg dose of [^{14}C]dexlansoprazole on day 5. **DDR** = Dual Delayed Release™; **SD** = standard deviation.

Table I. Pharmacokinetic parameter estimates of total radioactivity, dexlansoprazole, 5-hydroxy dexlansoprazole and dexlansoprazole sulfone in plasma on day 5 following 60 mg doses of dexlansoprazole DDR for 4 days and a single 60 mg dose of [14C]dexlansoprazole on day 5

Variable	t_{max} (h)	C_{max} (ng/mL)	AUC_{24} (ng • h/mL)	$t_{½z}$[a] (h)	CL/F (L/h)	V_z/F (L)	AUC_{24} ratio (%)[b]
Total radioactivity							
Mean all	1.50	1562	10 051	11.9 (7.27)	NA	NA	NA
SD	2.21	519	10 371	9.43	NA	NA	NA
Mean[c] EM	0.60	1375	5862	12.4 (6.94)	NA	NA	NA
SD	0.22	273	1680	10.5	NA	NA	NA
PM[d]	6.00	2497	30 998	9.51	NA	NA	NA
Dexlansoprazole							
Mean all	1.50	1176	6964	2.24 (1.64)	17.5	38.4	NA
SD	2.21	492	8588	1.93	11.9	19.3	NA
Mean[c] EM	0.60	1001	3507	1.46 (1.43)	20.5	41.8	NA
SD	0.22	270	1606	0.22	10.4	19.4	NA
PM[d]	6.00	2050	24 247	6.17	2.4	21.4	NA
5-Hydroxy dexlansoprazole							
Mean all	1.21	54.3	198	2.28 (1.84)	NA	NA	7.37
SD	1.40	36.9	110	1.49	NA	NA	6.94
Mean[c] EM	0.65	64.6	232	1.68 (1.63)	NA	NA	8.80
SD	0.34	30.2	82.2	0.34	NA	NA	6.67
PM[d]	4.00	2.97	30.2	5.26	NA	NA	0.10
Dexlansoprazole sulfone							
Mean all	1.50	57.0	919	7.88 (2.40)	NA	NA	4.22
SD	2.25	114	2192	10.6	NA	NA	8.83
Mean[c] EM	0.60	10.4	23.7	7.79 (2.10)	NA	NA	0.60
SD	0.52	5.07	18.0	11.8	NA	NA	0.23
PM[d]	6.00	290	5393	8.34	NA	NA	22.2

a Arithmetic mean (harmonic mean).

b (AUC_{24} metabolite/AUC_{24} dexlansoprazole) × 100%.

c Descriptive statistics for CYP2C19 extensive metabolizers (n = 5).

d Individual values for CYP2C19 poor metabolizer (n = 1).

AUC_{24} = area under the plasma concentration-time curve from time zero to 24 hours; **CL/F** = oral clearance; **C_{max}** = maximum plasma concentration; **CYP** = cytochrome P450; **DDR** = Dual Delayed Release™; **EM** = extensive metabolizer; **NA** = not applicable; **PM** = poor metabolizer; **SD** = standard deviation; **$t_{½z}$** = apparent terminal elimination-phase half-life; **t_{max}** = time to C_{max}; **V_z/F** = apparent volume of distribution during the terminal phase.

the radioactive dose excreted through 24 hours post-dose.

Metabolite profiles were determined from each subject's faecal sample that contained sufficient radioactivity over 96 hours post-dose, and are summarized in table IV. Unlike urine, no marked quantitative differences in faecal metabolites were noted between the EM subjects and the PM subject. Dexlansoprazole accounted for an average of approximately 23% of the total dose, with tentatively identified metabolites accounting for up to 72% of the radioactivity in faeces. The metabolites 5-hydroxy dexlansoprazole sulfide and dexlansoprazole sulfide were the main radioactive components detected, with other metabolites individually contributing ≤1.5% of the radioactive dose.

Safety

There were no deaths, serious AEs or premature discontinuations in this study. Two subjects

experienced one AE each, abdominal pain or diarrhoea, 4 days after the last dosing (dexlansoprazole DDR on days 1–4 and [^{14}C]dexlansoprazole on day 5). These AEs were of mild severity and were considered by the investigator not related to study drug. In addition, no subject had laboratory values, physical examinations, vital signs or ECGs that were considered by the investigator to be clinically significant or were reported as AEs.

Discussion

The ADME of dexlansoprazole was assessed in six healthy male subjects following multiple daily doses of 60 mg dexlansoprazole DDR for 4 days and a single 60 mg dose of [^{14}C]dexlansoprazole in Maalox® suspension on day 5. PPIs administered orally when unprotected from the acidic environment of the stomach, either a non-enteric-coated formulation or as an oral suspension or solution, are susceptible to degradation to a sulfenic acid.[13] In the current study, to ensure some degree of acid protection prior to administering the [^{14}C]dexlansoprazole dose, subjects were given commercially available dexlansoprazole DDR 60 mg capsules once daily for 4 days to raise intra-gastric pH > 4.[2] The drug product in the dexlansoprazole DDR capsules is currently protected from the acidic environment by enterically coating particles to release drug at higher pH, typically in the small intestine.[3] However, it is not practical to manufacture radiolabelled dexlansoprazole to mimic the DDR encapsulated formulation. Since PPIs can be administered in a buffered suspension,[14,15] day 5 dose of [^{14}C]dexlansoprazole was suspended in Maalox® in order to minimize degradation of the radiolabelled product in the acid environment of the stomach. Because dexlansoprazole has an acid dissociation constant (pK_a) of 4, it is expected to be soluble at the higher pH in the Maalox® vehicle. Mean plasma exposure (C_{max} and AUC values) and elimination ($t_{½}$ and oral clearance) of dexlansoprazole following administration of [^{14}C]dexlansoprazole in Maalox® on day 5 were generally similar to those observed from previous study data.[1,2,16] After a 60 mg [^{14}C]dexlansoprazole dose in Maalox®, mean dexlansoprazole C_{max} and AUC_{24} values of 1176 ± 492 ng/mL and 6964 ± 8588 ng • h/mL, respectively, from all six subjects were comparable to those obtained following multiple doses of dexlansoprazole DDR 60 mg (1434 ± 703 ng/mL and 6373 ± 4780 ng • h/mL, respectively).[2] These results indicate that the multiple-dose design and use of Maalox® as the dose vehicle afforded levels of acid protection comparable to that of the

Table II. Relative distribution of radioactivity in plasma at 0.25–16 hours (mean percent of plasma radioactivity [SD]) in EM and PM subjects

Variable	EM subjects (n = 5)			PM subject			
	0.25 h	2 h	6 h	0.25 h	2 h	6 h	16 h
Dexlansoprazole	88.51 (5.72)	80.97 (9.12)	70.12 (15.2)	99.61	92.46	88.81	71.23
5-Glucuronyloxy dexlansoprazole	3.69 (2.36)	8.82 (3.61)	7.92 (4.36)	0.00	0.08	0.18	0.13
5-Glucuronyloxy dexlansoprazole sulfide	0.03 (0.07)	0.80 (0.68)	6.76 (6.21)	0.00	0.00	0.11	0.13
4-Sulfonyloxy dexlansoprazole	0.04 (0.06)	0.80 (0.12)	0.91 (1.03)	0.00	0.32	0.65	0.25
5-Sulfonyloxy dexlansoprazole sulfide	0.00 (0.00)	0.12 (0.26)	1.11 (2.32)	0.00	0.00	0.00	0.00
5-Hydroxy dexlansoprazole	6.33 (4.20)	5.70 (4.12)	3.94 (3.29)	0.00	0.00	0.11	0.00
4-Sulfonyloxy dexlansoprazole sulfide	0.00 (0.00)	0.00 (0.00)	0.97 (1.22)	0.00	0.00	0.12	0.75
Dexlansoprazole sulfone	0.80 (0.52)	0.70 (0.43)	0.25 (0.35)	0.39	6.20	8.19	22.54
Dexlansoprazole sulfide	0.00 (0.00)	0.02 (0.04)	0.22 (0.30)	0.00	0.33	0.90	3.27
M2 unidentified	0.11 (0.13)	0.92 (0.36)	3.76 (3.11)	0.00	0.52	0.66	1.57
M25 unidentified	0.00 (0.00)	0.06 (0.09)	1.05 (2.35)	0.00	0.08	0.00	0.00
% Identified	99.40 (0.52)	97.94 (1.78)	92.20 (6.16)	100.0	99.40	99.07	98.30
% Chromatographed	99.50 (0.52)	98.93 (1.54)	97.01 (4.73)	100.0	100.0	99.73	99.87

EM = extensive metabolizer; **M** = metabolite; **PM** = poor metabolizer; **SD** = standard deviation.

Table III. Relative distribution of radioactivity in urine over 24 hours in EM and PM subjects

Variable	EM subjects (n = 5) [mean % (SD)]	PM subject (%)
2-S-*N*-acetylcysteinyl hydroxybenzimidazole	1.6 (1.3)	0.8
2-S-*N*-acetylcysteinyl benzimidazole	1.9 (0.8)	19.0
5-Glucuronyloxy dexlansoprazole	14.1 (1.2)	2.8
5-Glucuronyloxy dexlansoprazole sulfide	10.8 (0.7)	4.6
5-Sulfonyloxy dexlansoprazole sulfide	3.1 (1.1)	1.7
4-Sulfonyloxy dexlansoprazole	0.4 (0.2)	0.9
Identified radioactive components in urine (percent of urinary radioactivity)	86.1 (5.2)	80.9
Total radioactive components in urine (percent of dose)	37.2 (4.5)	36.9
Identified radioactive components in urine (percent of dose)	31.9 (2.5)	29.8

EM = extensive metabolizer; **PM** = poor metabolizer; **SD** = standard deviation.

DDR formulation, allowing for the quantitation of parent compound and metabolites in plasma, urine and faeces. While this liquid formulation lacks the modified-release characteristics of the DDR formulation that result in dual plasma peaks, the objective of this study was primarily to assess the ADME of [14C]dexlansoprazole and not to compare the effect of a change in formulation (suspension vs DDR capsule) on pharmacokinetic parameters. To meet this objective, plasma exposure of radiolabelled dexlansoprazole similar or comparable to that of the DDR formulation is needed, and results from the current study indicate that this was achieved.

The metabolism of most PPIs involves CYP2C19, a polymorphic enzyme. Frequency of the PM phenotype varies among different racial and ethnic populations.[7] Genotype results indicated that five subjects were phenotyped as CYP2C19 EM status and one subject was deemed a PM status. While it was fortunate that a subject was identified in this ADME study as a CYP2C19 PM, comparison of the pharmacokinetic and metabolism data based on metabolizer status was to illustrate the involvement of CYP2C19 in the metabolism of dexlansoprazole. In the case of dexlansoprazole, CYP2C19 is involved in the conversion of parent drug to 5-hydroxy dexlansoprazole, the primary first metabolic step. Thus it would be expected that metabolizer status would have an effect on pharmacokinetic parameters and the quantitative differences in metabolites detected in plasma and urine, as can clearly be seen. Total clearance of dexlansoprazole in the PM subject was approximately 12% that of the mean clearance in the EM subjects, and this difference in elimination likely resulted in greater plasma exposure of parent drug. Our results are similar to those reported in an earlier study examining the impact of CYP2C19 metabolizer status on the enantiomers of lansoprazole, of which dexlansoprazole is the *R* (+) enantiomer.[10] Mean AUC values of PM subjects (n = 6) were 4.6 times greater than those of EM subjects (n = 6), while oral clearance of PM subjects was 22% that of EM subjects.

Table IV. Relative distribution of radioactivity in faeces over 96 hours in male subjects

Variable	Male subjects (n = 6) [mean % (SD)]
Dexlansoprazole/5-hydroxy dexlansoprazole sulfide[a]	22.9 (4.6)
5-Sulfonyloxy dexlansoprazole sulfide	1.2 (2.7)
4-Sulfonyloxy dexlansoprazole sulfide	0.6 (0.8)
5-Hydroxy dexlansoprazole sulfone	0.9 (0.5)
4-Hydroxy dexlansoprazole sulfide	0.6 (0.5)
Dexlansoprazole sulfide	5.6 (1.0)
Identified radioactive components in faeces (percent of faecal radioactivity)	71.9 (4.1)
Total radioactive components in faeces (percent of dose)	44.4 (7.0)
Identified radioactive components in faeces (percent of dose)	32.0 (5.8)

a Mass spectral analysis showed that 5–hydroxy dexlansoprazole sulfide was the major co-eluting component.

SD = standard deviation.

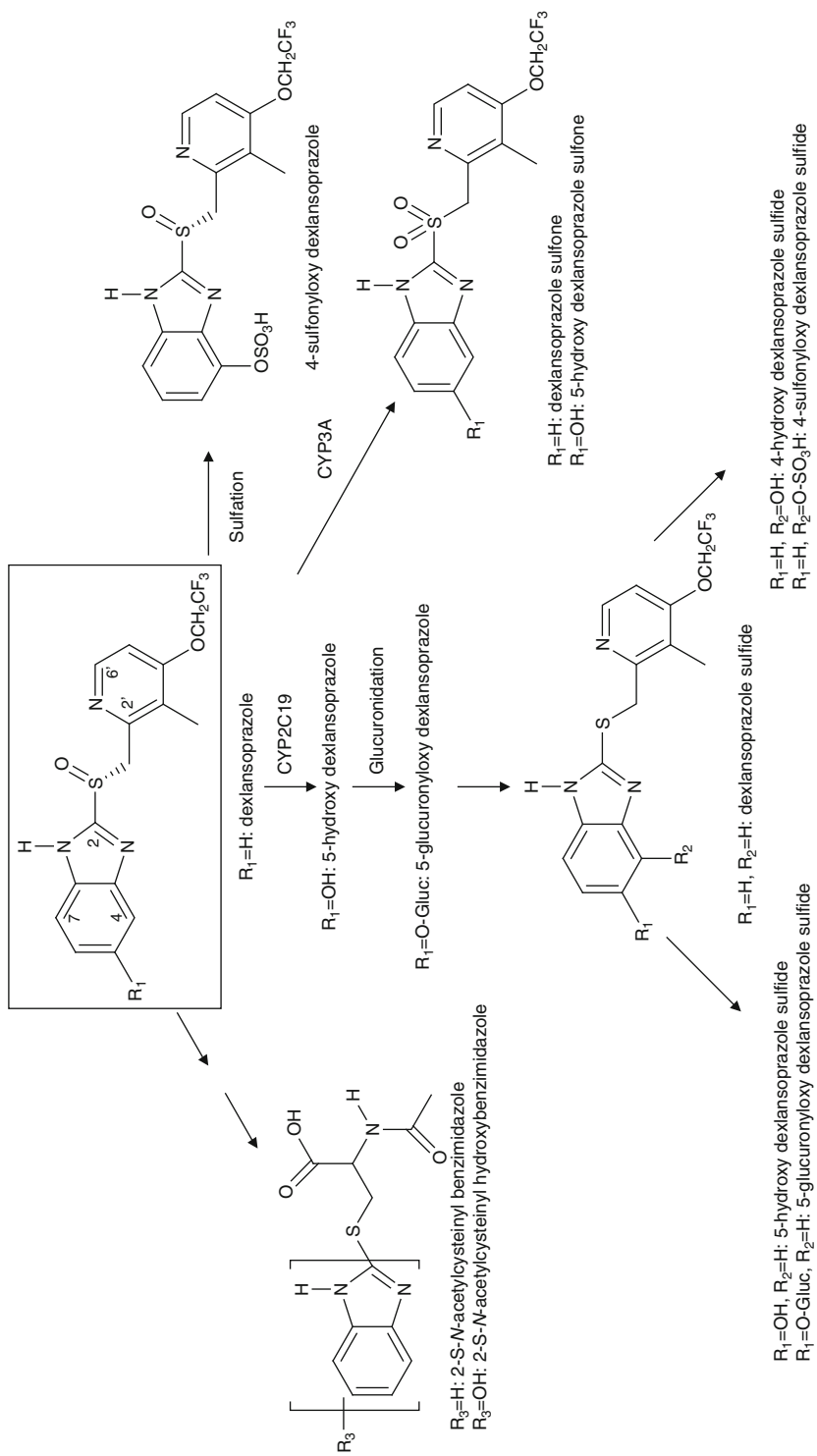

Fig. 4. Proposed metabolic pathways of dexlansoprazole in humans. **Gluc** = glucuronide.

Since oxidation of dexlansoprazole to 5-hydroxy dexlansoprazole occurs mainly via the CYP2C19 isozyme, plasma exposure (AUC) of this metabolite in the CYP2C19 PM subject was only 13% that of the mean value from EM subjects. Additionally, secondary metabolites such as glucuronyl and sulfonyl conjugates associated with 5-hydroxy dexlansoprazole were also present in lesser quantities in the plasma and urine from the PM subject compared with those of the EM subjects. Moreover, plasma exposure of dexlansoprazole sulfone, formed mainly via CYP3A, increased approximately 228-fold in the PM subject compared with EM subjects. The increase in dexlansoprazole sulfone plasma exposure was likely due to the decreased ability of the PM subject to form the 5-hydroxylated metabolite, as similar changes in lansoprazole, racemic mixture of S-lansoprazole and dexlansoprazole have been observed.[10] As a consequence, this decreased ability of the PM subject to metabolize dexlansoprazole to the 5-hydroxylated metabolite likely resulted in greater amounts of the *N*-acetylcysteinyl benzimidazole metabolite in urine.

The proposed metabolic pathways for dexlansoprazole in humans are generally similar to those in animals, involving oxidative, reductive and conjugative pathways, and are summarized in figure 4. Following oral administration of a 5 mg/kg single dose of [14C]dexlansoprazole to rats or dogs, recovery of radioactivity was greater in faeces than in urine. Approximately 69–81% and 53–83% of the administered radioactive dose was recovered in the faeces of rats and dogs, respectively.[5,6] Urinary recovery of [14C]dexlansoprazole-derived radioactivity ranged from approximately 15% to 25% in rats, and 28% to 30% in dogs. In our study with human subjects, faecal and urinary recoveries were roughly equal (48% and 51%, respectively). Dexlansoprazole is the *R*-enantiomer of lansoprazole and differences in the pharmacokinetics and rate of metabolism between enantiomers have been reported; however, qualitative differences in the metabolic profile for the major metabolites between lansoprazole and dexlansoprazole were not observed.[17,18]

Dexlansoprazole was the major component detected in plasma, with hydroxylation of the benzimidazole ring, particularly at the 5-position, appearing to be a major route of metabolism in rats and dogs.[5,6] In the rat, the major circulating metabolites were 5-sulfonyloxy dexlansoprazole sulfide and 4-glucuronyloxy dexlansoprazole sulfide, and in the dog dexlansoprazole sulfone, 5-glucuronyloxy dexlansoprazole and 5-glucuronyloxy dexlansoprazole sulfone. No measurable amounts of parent drug were detected in the urine, faeces or bile of rats or dogs. Glutathione-derived conjugates were the major metabolites in rat urine, whereas dexlansoprazole-derived glucuronide and sulfate conjugates were the major metabolites in dog urine. 5-Hydroxy dexlansoprazole sulfide was the major component in faeces, with dexlansoprazole-derived glucuronide and sulfate conjugates in bile.

Study strengths include the use of radiolabelled dexlansoprazole and the presence of a CYP2C19 PM to compare against the EM subjects. Study limitations are that the radiolabelled formulation used in this study was not the same as the DDR formulation, six healthy male subjects were enrolled in this ADME study with only one subject being a CYP2C19 PM, and the pharmacokinetics of dexlansoprazole was not determined on day 4 after multiple doses of the DDR formulation.

Conclusion

This study has shown that dexlansoprazole was well absorbed and extensively metabolized by oxidative, reductive and conjugative pathways, and excreted equally in urine and faeces to achieve mass balance. Dexlansoprazole demonstrated a favourable safety profile and was well tolerated in this study.

Acknowledgements

This study (T-P106-141) was presented at the 15th biennial meeting of the International Society for the Study of Xenobiotics-North America 2008, San Diego, CA, USA. The authors would like to thank John Brackett, PhD, of Takeda Global Research & Development Center, Inc, for formulation development of the radiolabelled dexlansoprazole in Maalox®. This study was sponsored by Takeda Global Research & Development Center, Inc, Deerfield, IL, USA. The study was conducted by TAP Pharmaceutical Products, Inc,

which is now a part of Takeda Global Research & Development Center, Inc. The study sponsor was involved in the design and conduct of the study and collection and management of the data. Ronald Lee is an employee of Takeda Global Research & Development Center, Inc, and Brian Grabowski was an employee of Takeda Global Research & Development Center, Inc, at the time the study was conducted. Both authors were involved in the design of the study, analysis and interpretation of the data, and the preparation, review and approval of this manuscript. Assistance in manuscript preparation was provided by Meryl Gersh, PhD, of AlphaBioCom, LLC, King of Prussia, PA, and funded by Takeda Pharmeceuticals USA, Inc.

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Correspondence: *Ronald Lee*, PhD, Takeda Global Research & Development Center, Inc, One Takeda Parkway, Deerfield, IL 60015, USA.
E-mail: ronald.lee@takeda.com