Expert Opinion

Dexlansoprazole MR

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Background: Proton pump inhibitors (PPIs) have been used for more than two decades to control symptoms of gastroesophageal illnesses. Studies have shown that most PPIs do not provide 24-h symptom control, and that can be the reason for treatment failure. Recently, dexlansoprazole dual delayed release™ (DDR) (Takeda Pharmaceuticals North America, Inc., USA) under the trade name of Kapidex™ (Takeda Pharmaceutical Company Limited, Japan) came onto the market to provide longer duration of action and more effective acid suppression. *Objective*: The purpose of this paper is to discuss the pharmacology of dexlansoprazole DDR and to provide a concise review of all available studies showing its efficacy. The combination of the slower metabolism of the R-enantiomer and novel dual release pharmacokinetics is impressive. *Methods*: This manuscript is based on a review of all currently available medical literature on dexlansoprazole DDR. *Conclusion*: Dexlansoprazole DDR has the potential to outperform traditional PPIs based on the metabolism and novel pharmacokinetics. It is currently FDA approved for the treatment of erosive esophagitis (acute, maintenance) and symptomatic gastroesophageal reflux disease.

Keywords: acid peptic disease, erosive esophagitis, Kapidex, proton pump inhibitors

Expert Opin. Pharmacother. (2009) **10**(14):2329-2336

1. Introduction

Proton pump inhibitors (PPIs) are very strong acid suppressants and are used in a wide variety of acid peptic disease. Several studies have shown that PPIs are often unable to control symptoms and provide 24-h control of acid secretion with a single daily oral dose [1,2,3]. Of the gastroesophageal reflux disease (GERD) patients on PPI therapy, 30% experience treatment failure [2,4]. Several factors are involved in PPI failure, including limitations in the pharmacokinetics (PK) of conventional PPI formulations, which provide a single drug release.

Several studies are being conducted to find a PPI that can provide a sustained effect over the 24-h interval between doses. Dexlansoprazole MR (modified release) (**Box 1**) with a Dual Delayed Release™ (DDR), commercially available as Kapidex™, was approved by the FDA on January 30, 2009. It is approved for once-daily treatment of heartburn associated with symptomatic non-erosive GERD, healing of erosive esophagitis (EE) and maintenance of healed EE. It is designed to prolong its plasma concentration-time profile, thus providing better symptom control over 24 h with once-daily use.

2. Background

Suppression of gastric acid secretion by PPIs is greatest when proton pumps are most active. Histamine and adrenocorticotropic hormone (ACTH) are two main secretagogues that bind to parietal cells and lead to activation of H-K ATPase enzyme (proton pumps), thereby stimulating acid secretion. In the basal state, gastric acid secretion is low due to inhibition of gastrin release by somatostatin released from D cells in the body and antrum. Cephalic (vagal mediated) and gastric

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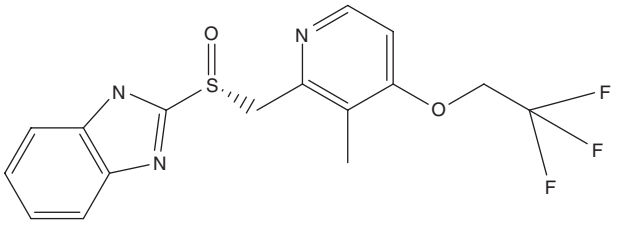
10.1517/14656560903198978 ISSN 1465-6566

Box 1. Drug summary.

Drug name	Dexlansoprazole
Phase	Launched
Indication	Oesophagitis Gastroesophageal reflux disease
Pharmacology description	H+ K+ transporting ATPase inhibitor
Route of administration	Alimentary, po
Chemical structure	
Pivotal trial(s)	It has undergone Phase III trials in the US in > 6000 patients with erosive oesophagitis and non-erosive GORD A Phase III trial in 165 GORD patients who had previously received bid PPI therapy is underway

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phase (antral distension and nutrient-mediated suppression of somatostatin leads to increased gastrin and histamine) lead to increased acid output and to the lowering of gastric pH [5].

Proton pump inhibitors irreversibly block the activated proton pumps. However, to be most effective PPIs must be present in high concentration when the pumps are stimulated [6,7]. It is estimated that conventional PPIs inhibits 70% of active pumps at steady state with once-daily dosing [6,8].

All conventional PPIs have a relatively short plasma half-life (1 – 2 h) and limited residence time in the systemic circulation [7]. Thus, with once-daily dosing, systemic exposure to PPIs tends to wane until there is no circulating PPI present in plasma during later stages of the 24-h interval.

Different approaches have been used to extend duration of acid control with PPIs. One approach is to increase the daily dose and administer once daily. However, the few studies that evaluated the effect of doubling the dose have shown minimal benefit [9,10]. The second approach is to increase frequency of conventional PPIs by administering them twice daily [11]. This approach has been shown to enhance acid control, but is associated with poor compliance. Once-daily dosing is the preferred mode of administration for patients.

Esomeprazole, the S-enantiomer of omeprazole, was the first enantiomer PPI [12]. It is metabolized more slowly than R-omeprazole, resulting in higher plasma concentration. Despite providing significantly greater acid control than omeprazole 20 mg, lansoprazole 30 mg, rabeprazole 20 mg or pantoprazole 40 mg, it maintained intragastric pH > 4 for only 58.43% of the day [13]. This led to a great deal of interest in finding a new PPI that has greater potency and longer half-life compared with conventional PPIs.

3. Dexlansoprazole MR

Dexlansoprazole MR is a novel modified-release formulation of dexlansoprazole, the R enantiomer of lansoprazole. Lansoprazole and its enantiomers are equipotent in inhibiting (H+, K+)-ATPase. However, the R-enantiomer of lansoprazole shows a slower clearance with corresponding higher circulating plasma concentrations and terminal elimination half-life compared with S-lansoprazole, leading to higher and more prolonged serum concentrations [14].

3.1 Pharmacology and structural formula

Dexlansoprazole is a white to nearly white crystalline powder that melts with decomposition at 140°C. It is freely soluble in dimethylformamide, methanol, dichloromethane, ethanol and ethyl acetate; soluble in acetonitrile; slightly soluble in ether; very slightly soluble in water; and practically insoluble in hexane [15]. Dexlansoprazole is stable when exposed to light. It is more stable in neutral and alkaline conditions than in acidic conditions (**Figure 1**).

3.2 Pharmacokinetics

Dexlansoprazole MR uses an innovative delivery system with DDR technology. This technology uses granules with different pH-dependent dissolution profiles designed to optimize drug release. All conventional PPI delivery systems use single release formulations (immediate or delayed). DDR technology is designed to provide an initial drug release in the proximal small intestine after 1 – 2 h of administration followed by another drug release at more distal regions of the small intestine several hours later [14-16]. Of the administered

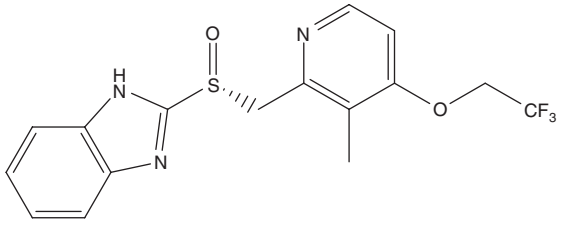

Figure 1. Dexlansoprazole MR.

drug, 25% is designed to release at pH 5.5 whereas the remaining 75% is designed to release at pH 6.75. As a result, dexlansoprazole MR produces a dual peaked PK profile, as opposed to the single peak seen with conventional PPIs (**Figure 2**).

Dexlansoprazole MR is designed to prolong the plasma concentration–time profile of dexlansoprazole and provide an extended duration of acid suppression, thereby increasing the mean intragastric pH > 4 over 24 h. Compared with lansoprazole, dexlansoprazole MR achieves higher AUCs without a commensurate increase in C_{max}. The DDR mechanism also prolongs the mean residence time (MRT; the average time a drug molecule spends in the systemic circulation) of dexlansoprazole. The MRT values for dexlansoprazole MR are 5.5 – 6.4 h compared with 2.8 – 3.0 h for conventional single release lansoprazole, demonstrating that the DDR formulation extends the duration of drug exposure by prolonging mean absorption time (MAT) [17].

A retrospective *post hoc* analysis and modeling by Wu and colleagues was conducted using data from three Phase I studies to determine threshold plasma concentration and to create a model that maximizes the relationship between the percentage time when intragastric pH > 4 and the percentage time that plasma concentrations are above a threshold value over a 24-h postdose interval. On the basis of this analysis, the mean percentage time when lansoprazole (30 mg) plasma concentrations were > 125 ng/ml was 17% compared to 34 – 50% for dexlansoprazole MR regimens (30 – 120 mg). Furthermore, the mean percentage time above the 125 ng/ml threshold for lansoprazole corresponded to an estimated percentage time of pH > 4 of 50% compared to 65 – 70% for dexlansoprazole MR. Dexlansoprazole MR maintained plasma drug concentration above this threshold ~ 2 – 3 times longer than lansoprazole. This difference seemed to provide greater percentage time when the pH was > 4 [16].

3.3 Absorption

After administration of dexlansoprazole MR 30 or 60 mg p.o. to healthy subjects and symptomatic GERD patients, mean C_{max} and AUC values of dexlansoprazole increased approximately dose proportionally [14].

Bioequivalence was demonstrated with dexlansoprazole MR administered as granules sprinkled over applesauce or as an intact capsule. The mean concentration versus time profile for the two regimens were nearly superimposable with the characteristic two plasma peaks resulting from the DDR technology [18].

3.4 Distribution

Plasma protein binding of dexlansoprazole ranged from 96.1 to 98.8% in healthy subjects and was independent of concentration from 0.01 to 20 mcg/mL. The apparent volume of distribution (Vz/F) after several doses in symptomatic GERD patients was 40.3 L [15].

3.5 Metabolism

Dexlansoprazole is extensively metabolized in the liver by oxidation, reduction and subsequent formation of sulfate, glucuronide and glutathione conjugates to inactive metabolites. Oxidative metabolites are formed by the CYP enzyme system including hydroxylation mainly by CYP2C19, and oxidation to the sulfone by CYP3A4 [14,15,19,20].

Dexlansoprazole is the chief circulating component in plasma regardless of CYP2C19 metabolizer status. In CYP2C19 intermediate and extensive metabolizers, the main plasma metabolites are 5-hydroxy dexlansoprazole and its glucuronide conjugate, while in CYP2C19 poor metabolizers dexlansoprazole sulfone is the chief plasma metabolite [15].

3.6 Elimination

Dexlansoprazole is eliminated with a half-life of ~ 1 – 2 h in healthy subjects and in patients with symptomatic GERD. No accumulation of dexlansoprazole occurs after multiple doses of dexlansoprazole MR 30 or 60 mg/day [14,15]. Following administration of dexlansoprazole MR, no unchanged dexlansoprazole is excreted in the urine. Following the administration of [14C] dexlansoprazole to six healthy male subjects, ~ 50.7% (standard deviation or SD: 9.0%) of the administered radioactivity was excreted in urine and 47.6% (SD: 7.3%) in the feces. Apparent clearance (CL/F) in healthy subjects was 11.4 – 11.6 L/h, respectively, after 5 days of 30 or 60 mg/day administration [15,21].

3.7 Effect of CYP2C19 polymorphism on systemic exposure of dexlansoprazole

Systemic exposure of dexlansoprazole is generally higher in intermediate and poor metabolizers. In Japanese male subjects who received a single dose of dexlansoprazole MR 30 or 60 mg (n = 2 – 6 subjects/group), mean dexlansoprazole C_{max} and AUC values were up to 2 times higher in intermediate compared to extensive metabolizers; in poor metabolizers, mean C_{max} was up to 4 times higher and mean AUC was up to 12 times higher compared to extensive metabolizers. Although this study was not conducted in Caucasians and African Americans, it is expected that dexlansoprazole exposure in these races will be affected by CYP2C19 phenotypes as well [15].

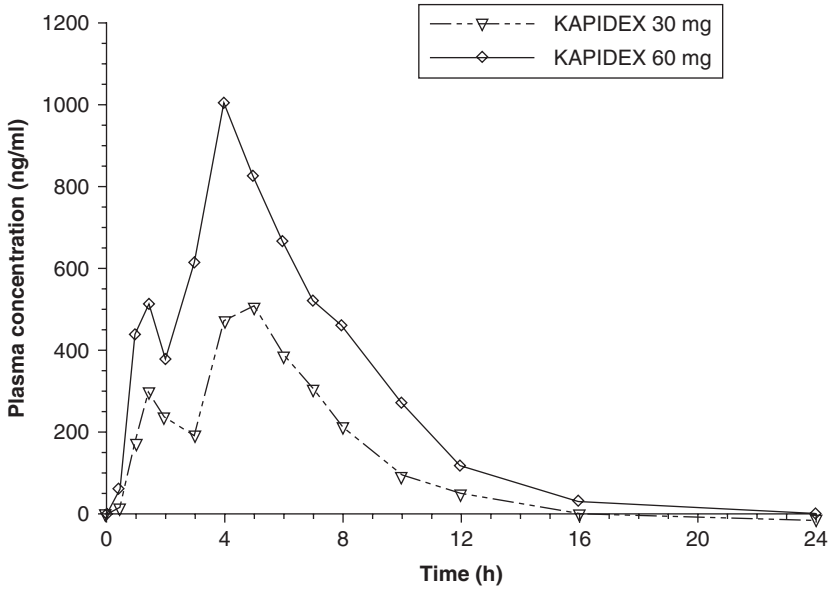

Figure 2. Mean plasma dexlansoprazole concentration–time profile following administration of Kapidex 30 or 60 mg/day p.o. for 5 days in healthy subjects [15].

3.8 Effect of food on pharmacokinetics and pharmacodynamics

In food-effect studies in healthy subjects receiving dexlansoprazole MR under various fed conditions compared to fasting, increases in C_{max} ranged from 12 to 55%, increases in AUC ranged from 9 to 37%, and t_{max} varied ranging from a decrease of 0.7 h to an increase of 3 h. No significant differences in mean intragastric pH were observed between fasted and various fed conditions. However, the percentage of time intragastric pH exceeded 4 over the 24-h dosing interval decreased slightly when dexlansoprazole MR was administered after a meal (57%) relative to fasting (64%), primarily due to a decreased response in intragastric pH during the first 4 h after dosing. Because of this, while dexlansoprazole MR can be taken without regard to food, some patients may benefit from administering the dose before a meal if post-meal symptoms do not resolve under post-fed conditions [15,20].

3.9 Pediatric use

The pharmacokinetics of dexlansoprazole in patients < 18 years of age have not been studied [15].

3.10 Geriatric use

The terminal elimination half-life of dexlansoprazole MR is significantly increased in geriatric subjects compared to younger subjects (2.23 and 1.5 h, respectively). This difference is not clinically relevant. Dexlansoprazole MR showed higher systemic exposure (AUC) in geriatric subjects (34.5% higher) than in younger subjects. No dose adjustment is needed in geriatric patients [22].

3.11 Renal impairment

Dexlansoprazole is extensively metabolized in the liver to inactive metabolites, and no parent drug is recovered in the urine following an oral dose of dexlansoprazole MR. Therefore, the pharmacokinetics of dexlansoprazole MR are not expected to be altered in patients with renal impairment, and no studies were conducted in subjects with renal impairment [15].

3.12 Hepatic impairment

In a study of 12 patients with moderately impaired hepatic function who received a single dose of dexlansoprazole MR 60 mg p.o., plasma exposure (AUC) of bound and unbound dexlansoprazole in the hepatic impairment group was ~ 2 times greater compared to subjects with normal hepatic function. This difference in exposure was not due to a difference in protein binding between the two liver function groups. No adjustment for dexlansoprazole MR is necessary for patients with mild hepatic impairment (Child-Pugh Class A). Dexlansoprazole MR 30 mg should be considered for patients with moderate hepatic impairment (Child-Pugh Class B). No studies have been conducted in patients with severe hepatic impairment (Child-Pugh Class C) [15,23].

3.13 Gender

In a study of 12 male and 12 female healthy subjects who received a single dose of dexlansoprazole MR 60 mg p.o., females had higher systemic exposure (AUC) (42.8% higher) than males [21]. No dosage adjustment is necessary in patients based on gender [15].

3.14 Carcinogenesis, mutagenesis, impairment of fertility

The carcinogenic potential of dexlansoprazole was assessed using lansoprazole studies. In two 24-month carcinogenicity studies, Sprague-Dawley rats were treated with lansoprazole at doses of 5 – 150 mg/kg/day p.o., ~ 1 – 40 times the exposure on a body surface (mg/m^2) on the basis of a 50-kg person of average height (1.46 m^2 body surface area (BSA)) given the recommended human dose of lansoprazole (30 mg/day) [15].

Lansoprazole produced dose-related gastric enterochromaffin-like cell (ECL) cell hyperplasia and ECL cell carcinoids in both male and female rats. It also increased the incidence of intestinal metaplasia of the gastric epithelium in both sexes [15].

A Phase I study compared the effect of dexlansoprazole MR with lansoprazole on serum gastrin level in healthy adults. On days 1 and 5, post-dose plasma gastrin (PG) level for the tow dexlansoprazole MR doses (90 and 120 mg) were similar and both levels were slightly higher than for lansoprazole. Day 8 and day 12 fasting PG values returned towards day 1 values for all regimens [21].

In male rats, lansoprazole produced a dose-related increase of testicular interstitial cell adenomas. The incidence of these adenomas in rats receiving doses of 15 – 150 mg/kg/day (4 – 40 times the recommended lansoprazole human dose based on BSA) exceeded the low background incidence (range = 1.4 – 10%) for this strain of rat. Testicular interstitial cell adenoma also occurred in 1 of 30 rats treated with lansoprazole 50 mg/kg/day (13 times the recommended lansoprazole human dose based on BSA) in a 1-year toxicity study [15].

Some studies showed increased incidence of liver tumors (hepatocellular adenoma plus carcinoma) in rats. The tumor incidences in male mice treated with lansoprazole 300 and 600 mg/kg/day (40 – 80 times the recommended lansoprazole human dose based on BSA) and female mice treated with lansoprazole 150 – 600 mg/kg/day (20 – 80 times the recommended human dose based on BSA) exceeded the ranges of background incidences in historical controls for this strain of mice [15].

Lansoprazole was negative in the Ames test, the *ex vivo* rat hepatocyte unscheduled DNA synthesis (UDS) test, the *in vivo* mouse micronucleus test and the rat bone marrow cell chromosomal aberration test. Lansoprazole was positive in *in vitro* human lymphocyte chromosomal aberration tests.

Dexlansoprazole was positive in the Ames test and in the *in vitro* chromosome aberration test using Chinese hamster lung cells. Dexlansoprazole was negative in the *in vivo* mouse micronucleus test.

The potential effects of dexlansoprazole on fertility and reproductive performance were assessed using lansoprazole studies. Lansoprazole at doses of ≤ 150 mg/kg/day p.o. (40 times the recommended lansoprazole human dose based on BSA) was not seen to have any effect on fertility and reproductive performance of male and female rats.

3.15 Drug interaction

Proton pump inhibitors undergo hepatic metabolism involving several CYP isoenzymes, particularly CYP3A and polymorphic CYP2C19. Few drug interactions have been associated with some PPIs such as lansoprazole, pantoprazole and rabeprazole because of their low affinity for certain hepatic CYP isoenzymes. However, omeprazole is rapidly and extensively metabolized by CYP3A and CYP2C19 and has been shown in well-controlled studies to reduce the clearance of drugs such as diazepam and phenytoin [24].

Dexlansoprazole *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 human hepatic CYP1A. Concomitant administration of dexlansoprazole MR with diazepam, phenytoin, warfarin or theophylline 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. Additionally, dexlansoprazole MR coadministered with warfarin did not affect the anticoagulant activity of warfarin [15].

4. Clinical studies

4.1 Healing of erosive esophagitis

Two multicenter, double-blind, active-controlled, randomized, 8-week studies were conducted in patients with endoscopically confirmed EE. Severity of the disease was classified based on the Los Angeles Classification Grading System (Grades A – D) [25]. Patients were randomized to one of the following three treatment groups: dexlansoprazole MR 60 mg/day, dexlansoprazole MR 90 mg/day or lansoprazole 30 mg/day.

Patients who were *Helicobacter pylori* positive or who had Barrett's esophagus and/or definite dysplastic changes at baseline were excluded from these studies. A total of 4,092 patients were enrolled and ranged in age from 18 to 90 years (median age 48 years) with 54% being male. Race was distributed as follows: 87% Caucasian, 5% black and 8% others. Based on the Los Angeles Classification, 71% of patients had mild EE (Grades A and B) and 29% had moderate-to-severe EE (Grades C and D) before treatment [15,25,26].

The studies were designed to test non-inferiority. If non-inferiority was demonstrated, then superiority would be tested. Although non-inferiority was demonstrated in both studies, the finding of superiority in one study was not replicated in the other. The proportion of patients with healed EE at week 4 or 8 is presented in **Table 1**.

4.2 Maintenance of healed erosive esophagitis

A multicenter, double-blind, placebo-controlled, randomized study was conducted in patients who successfully completed an EE study and showed endoscopically confirmed healed EE. Maintenance of healing and symptom resolution over a 6-month period was evaluated with dexlansoprazole MR 30 or 60 mg

Table 1. Healing rates for erosive esophagitis* (all grades) [15].

	No. of patients (*n*)‡	Treatment group (mg/day)	Week 4 percent healed	Week 8 percent healed§	(95% CI) for the treatment difference (Kapidex, lansoprazole) by week 8
Study 1	657	Dexlansoprazole MR (60)	70	87	(-1.5, 6.1)¶
	648	Lansoprazole (30)	65	85	
Study 2	639	Dexlansoprazole MR (60)	66	85	(2.2, 10.5)¶
	656	Lansoprazole (30)	65	79	

*Based on crude rate estimates, patients who did not have endoscopically documented healed erosive esophagitis and discontinued prematurely were considered not healed.
‡Patients with at least one post-baseline endoscopy.
§Primary efficacy endpoint.
¶Demonstrated non-inferiority to lansoprazole. Dexlansoprazole DDR 90 mg was studied and did not provide additional clinical benefit over Kapidex 60 mg.

Table 2. Maintenance rates* of healed erosive esophagitis at month 6 [15].

Number of patients (*n*)‡	Treatment group (mg/day)	Maintenance rate (%)
125	Dexlansoprazole MR (30)	66.4§
119	Placebo	14.3

*Based on crude rate estimates, patients who did not have endoscopically documented relapse and discontinued prematurely were considered to have relapsed.
‡Patients with at least one post-baseline endoscopy.
§Statistically significant versus placebo.

Table 3. Median percentages of 24-h heartburn-free periods during the 4 week treatment period of the symptomatic non-erosive GERD study [15].

Number of patients (*n*)	Treatment group (mg/day)	Heartburn-free 24-h periods (%)
312	Dexlansoprazole MR (30)	54.9*
310	Placebo	18.5

*Statistically significant versus placebo.
GERD: Gastroesophageal reflux disease.

once-daily compared to placebo [27]. A total of 445 patients were enrolled and ranged in age from 18 to 85 years (median age 49 years), with 52% being female. Race was distributed as follows: 90% Caucasian, 5% black and 5% others.

Of the patients treated with 30 mg of dexlansoprazole MR, 66% remained healed over the 6-month time period as confirmed by endoscopy (**Table 2**).

Dexlansoprazole MR 60 mg was studied and did not provide further clinical benefit over dexlansoprazole MR 30 mg. Dexlansoprazole MR 30 mg demonstrated a higher median percentage of 24-h heartburn-free days compared to placebo over the 6-month treatment period.

Howden *et al*. concluded from their study that dexlansoprazole MR 60 and 90 mg was statistically superior to placebo for maintaining healed EE and for controlling daytime and night-time heartburn [15,28].

4.3 Symptomatic non-erosive gastroesophageal reflux disease

A multicenter, double-blind, placebo-controlled, randomized, 4-week study was conducted in patients with a diagnosis of symptomatic non-erosive GERD made primarily by presentation of symptoms [29]. These patients, who identified heartburn as their primary symptom, had a history of heartburn for ≥ 6 months, had heartburn on ≥ 4 of 7 days immediately before randomization and had no esophageal erosions as confirmed by endoscopy. However, patients with symptoms that were not acid-related may not have been excluded using these inclusion criteria. Patients were randomized to one of the following treatment groups: dexlansoprazole MR 30 or 60 mg/day, or placebo. A total of 947 patients were enrolled and ranged in age from 18 to 86 years (median age 48 years) with 71% being female. Race was distributed as follows: 82% Caucasian, 14% black and 4% others.

Dexlansoprazole MR 30 mg provided statistically significantly greater percentage of days with heartburn-free 24-h periods over placebo as assessed by daily diary over 4 weeks. Dexlansoprazole MR 60 mg was studied and it provided no additional clinical benefit over dexlansoprazole MR 30 mg (**Table 3**) [15,29].

A higher percentage of patients on dexlansoprazole MR 30 mg had heartburn-free 24-h periods compared to placebo as early as the first 3 days of treatment and this was sustained throughout the treatment period (percentage of patients on day 3: dexlansoprazole MR 38% versus placebo 15%; on day 28: dexlansoprazole MR 63% versus placebo 40%).

5. Adverse reactions

The most commonly reported treatment-emergent adverse reactions (≥ 2%) that occurred at a higher incidence for dexlansoprazole MR than placebo in the controlled studies were diarrhea, abdominal pain, nausea, upper respiratory tract infection, vomiting and flatulence [15].

A Phase I study showed that single doses (90 and 300 mg p.o.) of dexlansoprazole did not prolong QT interval and were well tolerated in healthy subjects except for minor side effects like somnolence and headache [30].

6. Expert opinion

Dexlansoprazole MR is a new generation PPI that was recently approved by the FDA. It provides ≤ 24-h relief of GERD symptoms with a single dose administration. It has been shown to be effective in the management of healing and maintenance of healed EE. The DDR formulation technology of dexlansoprazole MR results in a plasma concentration–time profile characterized by two distinct peaks, leading to an extended duration of therapeutic plasma drug concentrations compared with conventional delayed release lansoprazole. Furthermore, dexlansoprazole MR maintains plasma drug concentrations above the threshold level longer than lansoprazole at all doses, resulting in an optimized drug exposure–intragastric pH relationship. Finally, dexlansoprazole MR, using DDR technology, increases the percentage of time intragastric pH is > 4 (drug level > 125 ng/ml) versus lansoprazole on day 5. The potential to replace twice-a-day PPIs with once-a-day use of dexlansoprazole MR has not been investigated yet.

Furthermore, the side-effect profile is comparable to that of other PPIs. This agent has the potential to enhance the treatment of patients with acid peptic disease through the DDR technology and selection of R-enantiomer. The drug is being marketed in the US at a per capsule discount of 25% below the price of esomeprazole, an excellent strategy in our current economic recession and health care reform arena.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

Bibliography

1. Katz PO, Scheiman JM, Barkun AN. Review article: acid-related disease-what are the unmet clinical needs? Aliment Pharmacol Ther 2006;23(2):9-22
2. Fass R, Shapiro M, Dekel R, Sewell J. Systematic review: proton-pump inhibitor failure in gastro-oesophageal reflux disease- where next? Aliment Pharmacol Ther 2005;22(2):79-94
3. Hunt RH. Review article: the unmet needs in delayed-release proton-pump inhibitor therapy in 2005. Aliment Pharmacol Ther 2005;22(3):10-19
4. Carlsson R, Dent J, Watts R, et al. Gastro-oesophageal reflux disease in Primary care: an international study of different treatment strategies with omeprazole. International GORD Study Group. Eur J Gastroenterol Hepatol 1998;10(2):119-24
5. Feldman M. Gastric Secretion. In Sleisenger & Fordtran's gastrointestinal and liver disease. 8th edition. Philadelphia, PA: Saunders Elsevier; 2006
6. Sachs G, Shin JM, Briving C, et al. The pharmacology of the gastric acid pump: the H+, K+ ATPase. Ann Rev Pharmacol Toxicol 1995;35:277-305
7. Sachs G, Shin JM, Howden CW. Review article: the clinical pharmacology of proton pump inhibitors. Aliment Pharmacol Ther 2006;23(2):2-8
8. Tonini M, DeGiorgio R, DePonti F. Novel therapeutic strategies in acid- related disorders. Expert Opin Ther Patents 2003;13(5):639-49
9. Fass R, Murthy U, Hayden CW, et al. Omeprazole 40 mg once a day is equally effective as lansoprazole 30 mg twice a day in symptom control of patients with gastro-oesophageal reflux disease (GERD) who are resistant to conventional-dose lansoprazole therapy-a prospective, randomized, multi-centre study. Aliment Pharmacol Ther 2000;14(12):1595-603
10. Bate CM, Booth SN, Crowe JP, et al. Does 40 mg omeprazole daily offer additional benefit over 20 mg daily in patients requiring more than 4 weeks of treatment for symptomatic reflux oesophagitis? Aliment Pharmacol Ther 1993;7(5);501-7
11. Kuo B, Castell DO. Optimal dosing of omeprazole 40 mg daily: effects on gastric and esophageal pH and serum gastrin in healthy controls. Am J Gastroenterol 1996;91(8):1532-8
12. Abelo A, Andersson TB, Antonsson M, et al. Stereoselective metabolism of omeprazole by human cytochrome P450 enzymes. Drug Metab Dispos 2000;28(8):966-72
13. Miner P, Katz P, Chen Y, Sostek M. Gastric acid control with esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole: a five-way crossover study. Am J Gastroenterol 2003;98(12):2616-20
14. Vakily M, Zhang W, Wu J, et al. Pharmacokinetics and pharmacodynamics of a known active PPI with a novel dual delayed release technology, dexlansoprazole MR: a combined analysis of randomized controlled clinical trials *. Curr Med Res Opin 2009;25:627-38
15. Kapidex package insert. (Takeda Global Research & Development Center, Inc)
16. Wu J, Vakily M, Witt G, et al. TAK-390 MR vs. Lansoprazole (LAN) for maintenance of drug concentration above a threshold which corresponds to higher%-time pH>4. Am J Gastroenterol 2007;102(Suppl 2):124. (ID 55076)
17. Metz DC, Vakily M, Dixit T, Mulford D. Review article: dual delayed release formulation of Dexlansoprazole MR. A novel approach to outcome the limitations of conventional single release proton pump inhibitor therapy. Aliment Pharmacol Ther 2009;29(9):928-37
18. Czerniak R, Vakily M, Wu J. TAK-390 MR, a novel dual delayed release formulation of a PPI, is bioequivalent when administered as granules sprinkled over applesauce or as an intact capsule.

Am J Gastroenterol 2008;103 (Suppl S):S4-5. (ID: 58627)

19. Grabowski B, Lee R, Czerniak R. Metabolism and excretion of (14 C) TAK- 390 in healthy male subjects. Drug Metab Rev 2008;40(Suppl 3):194-5
20. Lee RD, Vakily M, Mulford D, et al. Clinical trial: the effect and timing of food on the pharmacokinetics and pharmacodynamics of dexlansoprazole MR, a novel dual delayed release formulation of a proton pump inhibitor–evidence for dosing flexibility. Aliment Pharmacol Ther 2009;29:824-33
21. Vakily M, Lee RD, Wu J, et al. 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. Clin Drug Investig 2009;29:35-50
22. Vakily M, Zhang W, Wu J, Mulford D. Effect of age and gender on the pharmacokinetics of a single oral dose of TAK-390 MR (modified release). Clin Pharmacol Ther 2008;83(Suppl 1):96
23. Lee RD, Wu J, Vakily D, Mulford D. Effect of hepatic impairment on the pharmacokinetics of TAK-390 MR (modified release). Clin Pharmacol Ther 2008;83(Suppl 1)
24. Zhang W, Wu J, Atkinson SN. Effects of dexlansoprazole MR, a novel dual delayed release formulation of a proton pump inhibitor, on plasma gastrin levels in healthy subjects. J Clin Pharmacol 2009;49(4):444-54
25. Sharma P, Shaheen NJ, Perez MC, et al. Clinical trials: healing of erosive oesophagitis with dexlansoprazole MR, a proton pump inhibitor with a novel dual delayed-release formulation-results from two randomized controlled studies. Aliment Pharmacol Ther 2009;29:731-41
26. Shaheen N, Peura D, Perez MC, et al. Impact of baseline LA grade on healing on healing of erosive esophagitis (EE) following treament with TAK-390 MR, a proton pump inhibitor (PPI) with a novel dual delayed release formulation, compared with lansoprazole. Am J Gastroenterol 2008;103(1):S10-1
27. Metz DC, Howden CW, Perez MC, et al. Clinical trial: dexlansoprazole MR, a proton pump inhibitor with dual delayed-release technology, effectively controls symptoms and prevents relapse in patients with healed erosive oesophagitis. Aliment Pharmacol Ther 2009;29:742-54
28. Howden C, Larson L, Palmer R, Perez MC. Placebo controlled trial of 2 doses of TAK-390 MR a PPI with novel dual delayed release technology as maintenance treatment for patients with healed erosive esophagitis. Am J Gastroenterol 2008;103(1):abstract 13
29. Fass R, Chey WD, Zakko SF, et al. Clinical trial: the effects of the proton pump inhibitor dexlansoprazole MR on daytime and nighttime heartburn in patients with nonerosive reflux disease. Aliment Pharmacol Ther 2009;29(12):1261-72
30. Vakily M, Jingtao WU, Stuart N, et al. Lack of electrocardiographic effect of Dexlansoprazole MR, a novel modified-release formulation of the proton pump inhibitor Dexlansoprazole in healthy subjects. J Clin Pharmacol 2009. In Press

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