EXPERT REVIEWS

Dexlansoprazole MR for the management of gastroesophageal reflux disease

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Dexlansoprazole modified release (MR; Dexilant™), the *R*-enantiomer of lansoprazole, was approved in the USA in 2009 for the management of erosive esophagitis and nonerosive reflux disease. Dexlansoprazole MR has a unique dual delayed-release delivery system that was designed to address unmet needs that may accompany the use of single-release proton pump inhibitors (PPIs), specifically, their short plasma half-life and requirement for meal-associated dosing. The delivery technology of dexlansoprazole MR is designed to release the drug in two separate pH-dependent phases, the first in the proximal duodenum and the second in the more distal small intestine. This extends plasma concentration and pharmacodynamic effects of dexlansoprazole MR beyond those of single-release PPIs and allows for dosing at any time of the day without regard to meals. This added convenience, along with excellent healing of esophagitis and symptom relief, substantiate its use in patients with gastroesophageal reflux disease requiring PPI treatment.

Keywords: delayed release • dexlansoprazole MR • erosive esophagitis • GERD • proton pump inhibitor

Gastroesophageal reflux disease (GERD) affects approximately 20–40 million people in the USA and is a common cause of gastrointestinal (GI)-related morbidity [1]. GERD is characterized by the retrograde flow of gastric contents into the esophagus, most often manifesting as burning retrosternal chest pain and/or regurgitation. Up to 20% of adults in the USA report GERD symptoms at least twice weekly. More than half of patients with GERD report nocturnal symptoms, which are generally more difficult to control than daytime symptoms. The overall incidence of GERD in the USA is expected to increase as the population ages, becomes more overweight, and embraces a less healthy diet and/or lifestyle.

Medical therapy for GERD typically focuses on addressing inappropriate diet and lifestyle factors and reducing gastric acid production [2,3]. The most commonly used antisecretory agents include histamine-2 receptor antagonists (H2RAs) and proton pump inhibitors (PPIs). H2RAs have a fairly rapid onset of action and result in good symptom control, but are limited by tachyphylaxis and brief duration of action. They have limited effect on healing of erosive esophagitis (EE), especially more severe grades of mucosal damage. Compared with H2RAs, PPIs are associated with more robust and durable acid suppression. PPIs reduce acid production by binding to activated proton pumps located on parietal cells, rendering them nonfunctional. Omeprazole was the first PPI available for use in the USA, approved in 1989. Since that time, six other PPIs have been approved in the USA and have become one of the most commonly prescribed classes of medications in the world. PPIs have limitations including incomplete clinical effect in some patients, particularly if the medication is not taken appropriately. In addition, PPIs are more expensive than antacids and H2RAs, and frequently require escalation of dosing due to persistent symptoms with once-daily dosing. Since PPIs inhibit only active pumps and meals are the major physiologic stimulus for pump activation, conventional single-release PPIs need to be taken 30–60 min prior to mealtime, a schedule which patients often find difficult to adhere to. In addition, plasma half-life of PPIs is short, several hours at most,

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which leads to limited pharmacodynamic action later in the day as new pumps are generated and more pumps are stimulated by subsequent meals. Improper dosing and short plasma half-life are the major reasons patients have breakthrough symptoms on PPI therapy.

Overview of the market

While PPIs are the most effective class of drugs currently available to manage GERD, they do have inherent pharmacologic limitations that can lead to incomplete clinical response. They are acid-labile compounds so must be protected from degradation in the stomach either by enteric coating or buffering. After passing through the stomach, PPIs are rapidly absorbed and subsequently eliminated by the hepatic metabolism and renal excretion. The plasma half-life of a single-release PPI is short, which provides a limited window of opportunity surrounding mealtime for inhibition of active acid pumps. Because of this, PPIs are unable to completely control gastric pH over a 24-h period, unless they are taken multiple-times daily [4].

Dexlansoprazole modified release (MR) was designed specifically to meet this need by prolonging PPI pharmacokinetic and pharmacodynamic profiles. By using the more slowly metabolized *R*-enantiomer of its racemic parent, lansoprazole, and engineering a mechanism allowing the release of the drug twice, plasma residence time with dexlansoprazole MR 60 mg is nearly double [5] and pH control >4 is 18% greater compared with lansoprazole 30 mg [6].

Currently, an extended-release formulation of rabeprazole is under review by the US FDA. Each extended-release rabeprazole 50-mg capsule contains one 10-mg enteric-coated tablet and four 10-mg pulse-release tablets, which deliver medication in the small intestine and colon [7]. This formulation demonstrates a significant increase in the percentage gastric pH control >4.0 in a 24-h period compared with esomeprazole 40 mg and the conventional rabeprazole 20-mg delayed-release formulation, and comparable healing of severe EE as esomeprazole 40 mg [8].

Introduction to the drug

Dexlansoprazole is the *R*-enantiomer of lansoprazole, a PPI initially approved for use in the USA in 1995. Lansoprazole is a racemic mixture of equal proportions *R*-lansoprazole and *S*-lansoprazole. The *R*-enantiomer is associated with decreased clearance compared with the *S*-enantiomer, thus dexlansoprazole has increased systemic exposure compared with lansoprazole [9,10]. Dexlansoprazole is associated with three- to five-fold greater area under the plasma drug concentration time curve (AUC) compared with *S*-lansoprazole. It is highly protein bound and its elimination is through hepatic biotransformation to oxidative metabolites by CYP2C19 and CYP3A4 with subsequent conjugation to inactive products and elimination in the urine and feces. The drug does not appear to be eliminated unchanged in the urine.

The elimination half-life of dexlansoprazole is approximately 1–2 h, which is similar to other PPIs. The dual delayed-release technology employed to deliver dexlansoprazole is more important in prolonging its plasma residence time than its inherently slower hepatic clearance. The delivery system distributes drug to the proximal and more distal small intestine by two distinct pH-dependent releases of medication. After dissolution of the outer capsule, the first set of granules (~25% of drug dose) is designed to release quickly in the proximal duodenum (at pH 5.5). This provides an initial peak in plasma dexlansoprazole concentration within 1–2 h of capsule ingestion similar to that of lansoprazole and other single-release PPIs. The second release of remaining granules (~75% of drug dose) is designed to occur further along the GI tract (at pH 6.75) and creates a second peak in plasma dexlansoprazole concentrations within 4–5 h of capsule ingestion. This second release provides more drug for absorption later in the dosing interval to extended duration of acid suppression. Thus, the resulting time–concentration profile of dexlansoprazole MR has a two-peaked pattern that extends up to 12 h after the drug is ingested.

PPI chemistry

Proton pump inhibitors work by covalently and irreversibly binding to cysteine residues on the proton pump, thereby blocking the final step of acid production. Inhibited pumps remain nonfunctional and acid-secretory activity resumes only when new pumps are synthesized. Only two-thirds of proton pumps are inhibited by a single PPI dose, which leaves up to one-third of pumps uninhibited and subsequently able to secrete acid. Only active pumps can be inhibited by PPIs, and physiologic pump activation occurs with a meal. Because only 75% of pumps are activated by a single meal, subsequent food intake permits activation of dormant pumps. All PPIs share the same mechanism of action and have short half-lives (~1–2 h), so activation of proton pumps with acid secretion can occur after their plasma concentrations diminish to subtherapeutic levels. Because food is the primary stimulus for proton pump activation, administration of PPIs is commonly recommended a short time (30–60 min) before a meal, usually breakfast. The requirement to take medication within 60 min prior to food is problematic for many patients who do not eat regular meals, especially breakfast. Suboptimal dosing is therefore quite common and results in less consistent clinical efficacy.

Pharmacodynamics

Dexlansoprazole MR inhibits both basal and stimulated gastric acid production [11]. Two studies evaluated the pharmacodynamic effect (measured as intragastric pH) in subjects who had previously received 30, 60, 90 or 120 mg dexlansoprazole MR [6,12]. These studies indicated that doses less than 30 mg could result in therapeutically suboptimal intragastric pH control, while doses more than 90 mg would unlikely provide additional clinically meaningful pharmacologic benefit. Therefore, clinical development of dexlansoprazole MR proceeded with 30-, 60- and 90-mg doses but ultimately the 30-mg and 60-mg doses were approved for clinical use.

After 5 days of once-daily dosing, dexlansoprazole MR effectively suppresses gastric acid production [6]. Compared with lansoprazole 30 mg daily, dexlansoprazole MR 60 mg daily was associated with higher mean gastric pH [13,14] and proportion of time with gastric pH >4 [13,14]. The mean 24-h intragastric pH with dexlansoprazole MR 60 mg was 4.55 and was 4.13

with lansoprazole 30 mg. At day 5, the proportion of time that 24-h intragastric pH was >4 was 71% with dexlansoprazole MR 60 mg compared with 60% with lansoprazole 30 mg daily. No comparative data are available for dexlansoprazole MR 30 mg.

The impact of food on pharmacodynamics of dexlansoprazole MR was evaluated in healthy subjects during a randomized, open-label, crossover study. Placebo was administered after a 10-h fast, 30 min before, 5 min before or 30 min after a high-fat breakfast on day 1, and dexlansoprazole MR was given for each crossover period on day 3 [15]. Plasma concentrations of dexlansoprazole were measured on day 3 and 24-h intragastric pH was assessed on days 1 and 3. There were no clinically meaningful differences in pharmacodynamic parameters between any of the periods (mean 24-h intragastric pH and percent time 24-h intragastric pH was >4), implying both a lack of food effect and a lack of effect of timing of food intake relative to dosing with dexlansoprazole MR on intragastric pH profile [15].

A second study was designed to determine if dexlansoprazole MR could be taken at different times during the day. Pharmacodynamic parameters were assessed during a four-period, randomized crossover study in which subjects received drug daily for 5 days 30 min before breakfast, lunch, dinner or a bedtime snack [16]. While slight differences were found in mean 24-h intragastric pH between dosing at breakfast versus at lunch (0.2 difference in pH) and in the percentage of time 24-h intragastric pH >4 between dosing at breakfast versus at bedtime snack (7% difference), these were not considered to be clinically meaningful. No other significant differences in 24-h intragastric pH were found between breakfast and the other mealtimes [16].

Pharmacokinetics & metabolism

Dexlansoprazole MR demonstrates dose-proportional increases with respect to mean maximum plasma concentration (C_{max}) and AUC. No accumulation of drug occurs after multiple, once-daily doses of 30 or 60 mg although mean AUC and C_{max} values are slightly higher (<10%) on day 5 than on day 1, which suggests that dexlansoprazole MR exhibits time-independent pharmacokinetics [6,12].

A retrospective comparison of dexlansoprazole MR 60 mg and lansoprazole 60 mg demonstrated that the plasma concentration–time profile for dexlansoprazole MR 60 mg was characterized by two distinct peaks [17]. The first peak occurred 1–2 h after dosing, similar to the T_{max} of lansoprazole 60 mg, while the second peak occurred 4–5 h after dosing. Compared with lansoprazole, dexlansoprazole MR achieved higher AUCs without a concomitant increase in C_{max}. Mean residence time for dexlansoprazole MR 60 mg (5.5 h) was nearly twice that for lansoprazole 60 mg (2.9 h), demonstrating the extended duration of drug exposure. Longer mean residence time for dexlansoprazole MR is likely owing to its dual delayed-release technology; however, a relative contribution of enantiomeric difference cannot be ruled out [17].

Pharmacokinetics of dexlansoprazole MR in various fed conditions and at different mealtimes were evaluated in the studies discussed in the pharmacodynamics section earlier [15,16]. When compared with the fasted state, bioavailability (C_{max} and AUC) of the drug was actually slightly increased in the fed states. Systemic exposure of dexlansoprazole MR when dosed before breakfast was bioequivalent to when dosed before lunch, dinner or an evening snack [15,16]. Thus, dexlansoprazole MR can be taken without regard to food or timing of meals.

Administration of an intact dexlansoprazole MR capsule was compared with opening the capsule and sprinkling the contents over apple sauce [18]. No significant differences in either AUC or C_{max} were found between the two methods and bioequivalence was established for dexlansoprazole MR regardless of whether it was taken as an intact capsule or after being sprinkled on apple sauce [18].

Dexlansoprazole is metabolized in the liver via the cytochrome P450 (CYP) isoenzymes CYP2C19 and CYP3A4 [14]. Following oral administration of [C_{14}] dexlansoprazole MR to healthy volunteers, 51% was eliminated in urine and 48% in feces [14].

Coadministration of dexlansoprazole MR with warfarin did not effect the pharmacokinetics of warfarin or the international normalized ratio [14,19]. Dexlansoprazole MR produced no clinically significant effects on pharmacokinetics of diazepam, phenytoin and theophylline.

Despite a recent FDA warning, debate continues whether or not there is a meaningful interaction between PPIs and clopidogrel [20–24]. A study evaluating the effects of dexlansoprazole MR and other PPIs on the pharmacokinetics and pharmacodynamics of clopidogrel was recently reported in abstract form [25,26]. While dexlansoprazole MR was associated with a decrease in the peak plasma concentration of clopidogrel active metabolite, it does not significantly decrease the AUC for clopidogrel active metabolites and does not significantly interfere with clopidogrel action on platelet function [25]. While there are as yet no peer-reviewed data for dexlansoprazole MR and clopidogrel, clinical studies have shown that dexlansoprazole MR coadministration does not affect the pharmacokinetics of drugs that are metabolized by CYP2C19, such as phenytoin and diazepam [19], and thus it is not expected to cause the interactions found with clopidogrel and other PPIs, such as omeprazole.

Caution should be used when administering dexlansoprazole MR with drugs with pH-dependent absorption (iron, digoxin, ampicillin, ketoconazole), tacrolimus (where dexlansoprazole MR may decrease tacrolimus levels) and it should not be coadministered with atazanavir [14].

No dosing adjustments are needed in patients with renal impairment or in patients with mild hepatic impairment, but in those with moderate (Child–Pugh class B) hepatic impairment exposure is increased and thus the 30-mg dose should be considered in these patients. Dexlansoprazole MR has not been studied in patients with severe (Child–Pugh class C) cirrhosis [14].

Dexlansoprazole MR has a pregnancy category B, which indicates that there has been no documented toxicity in human studies. However, there is no published data specifically evaluating dexlansoprazole MR in pregnant women [14].

Clinical efficacy

Dexlansoprazole MR has been found to be effective at healing [27] and maintenance of healing [11] of EE, as well as the treatment of symptomatic nonerosive reflux disease [10] in adult

patients. Based on the results of these studies, dexlansoprazole MR received FDA approval for the healing of EE (dose 60 mg once daily), maintaining healing of EE (30 mg once daily) and treating symptomatic nonerosive reflux disease (30 mg once daily). An additional study also showed 30-mg dexlansoprazole MR to be effective at treating nocturnal heartburn and GERD-related sleep disturbance [28].

Dexlansoprazole MR in erosive esophagitis

The role of dexlansoprazole MR in the healing of EE was evaluated in two large, identical Phase III noninferiority trials, which were reported separately in the same publication [27]. Eligible patients with all grades of endoscopically proven EE (~30% of individuals had moderate or severe Los Angeles [LA] grade C or D esophagitis) were randomized to receive 8 weeks of dexlansoprazole MR 60 mg (n = 680 and 694) or 90 mg (n = 668 and 687), or lansoprazole 30 mg (n = 690 and 673) once daily. The primary end point was the proportion of patients with complete healing of EE at 8 weeks determined by life-table analysis in the intent-to-treat population. Secondary end points included the percentage of subjects with LA grades C and D EE healing at 8 weeks, and all-grade esophagitis healing at 4 weeks [27].

Overall, esophagitis healing rates with dexlansoprazole MR were 92–95% and 86–92% with lansoprazole at week 8. Using crude rate analysis, individual study results showed that esophagitis healing rates at week 8 for both 60- and 90-mg dexlansoprazole MR doses were superior to lansoprazole in one study (study 1) while 60-mg dexlansoprazole MR was noninferior and 90 mg was superior to lansoprazole in the other study. Healing at week 4 was comparable (>64%) for all treatments. Healing of moderate-to-severe esophagitis was significantly greater with dexlansoprazole MR 60 mg than lansoprazole in study 1, while both doses were noninferior to lansoprazole in study 2 [27]. A combined analysis of 8-week healing in patients with moderate-to-severe esophagitis showed dexlansoprazole MR 90 mg to be superior to lansoprazole. The median percentage of 24-h heartburn-free days was >80% in patients in all treatment groups [27].

Individuals who successfully completed either of the two healing studies mentioned previously were offered the opportunity to enroll in one of two placebo-controlled 6-month endoscopic maintenance of healing studies. One study evaluated dexlansoprazole MR 30 and 60 mg [11] and the other, 60-mg and 90-mg doses [29]. The primary efficacy end point was the proportion of subjects who maintained healed EE at 6 months. Secondary efficacy end points included the percentage of 24-h days without heartburn and the percentage of nights without heartburn. Almost 900 patients participated in these studies where relapse of EE was significantly greater (86%) in the placebo groups than in each dexlansoprazole MR groups (34%). Efficacy was similar for all three dexlansoprazole MR doses. In both studies for a period of up to 6 months, dexlansoprazole MR was superior in controlling symptoms of heartburn with median percentages of heartburn-free 24-h days of 96% and heartburn-free nights of 99% [29].

Dexlansoprazole MR in nonerosive reflux disease

Dexlansoprazole MR was evaluated in a Phase III trial of adult patients with nonerosive reflux disease [10]. Patients (n = 947) with typical heartburn symptoms and no endoscopic evidence of EE were randomized to dexlansoprazole MR 30 mg (n = 315) or 60 mg (n = 315) or placebo (n = 317) once daily for 4 weeks. The primary end point was the percentage of 24-h heartburn-free days over the 4-week treatment period.

Both dexlansoprazole MR doses were superior to placebo, with significantly greater median percentage of heartburn-free days than placebo (60 mg = 50%; 30 mg = 55% vs placebo = 19%) [12]. Night-time symptoms were significantly reduced in the dexlansoprazole groups (60 mg = 77%; 30 mg = 81% vs placebo = 52%) [10]. The severity of heartburn was also reduced in the dexlansoprazole MR groups.

A recent study randomized 305 patients with moderate-to-severe night-time heartburn and associated disturbed sleep to dexlansoprazole MR 30 mg or placebo once daily for 4 weeks [28]. The primary end point was the percentage of nights without heartburn. Secondary end points were the percentage of patients with relief of nocturnal heartburn and GERD-related sleep disturbances over the last 7 days of treatment. Dexlansoprazole MR 30 mg was superior to placebo in median percentage of nights without heartburn (73.1 vs 35.7%, respectively). Significantly, more dexlansoprazole MR-treated than placebo-treated patients obtained relief of nocturnal heartburn and GERD-related disturbed sleep (47.5 vs 19.6%, 69.7 vs 47.9%, respectively) [28]. The authors concluded that dexlansoprazole MR is effective in providing relief of nocturnal heartburn.

Postmarketing surveillance

Adverse events (AEs) have been reported in the postmarketing setting. As with other PPIs, severe reactions including Stevens–Johnson syndrome, toxic epidermal necrolysis and anaphylaxis have been reported, although the frequency of these events is uncertain, and causality has not always been established.

Safety & tolerability

Pooled safety data AEs, changes in clinical parameters, laboratory results and gastric histology) from >4000 patients involved in dexlansoprazole MR clinical trials has been reported. In these studies, patients received dexlansoprazole MR 30 mg (n = 455), 60 mg (n = 2311) or 90 mg (n = 1864), lansoprazole 30 mg (n = 1363) or placebo (n = 896) [30]. The number of patients with one or more treatment-emergent AEs per 100 patient-months of drug exposure was higher in the placebo (24%) and lansoprazole (21%) groups than in any dexlansoprazole MR (16–19%) group. Fewer patients receiving dexlansoprazole MR discontinued therapy because of an AE. Serum gastrin rose in all groups except placebo but increases were not dose-related. No concerning abnormalities were seen in gastric biopsies, nor were endocrine cell hyperplasia, dysplasia or neoplasia noted [30]. The authors concluded that dexlansoprazole MR had a safety profile similar to lansoprazole.

During a 12-month open-label safety trial, 591 GERD patients received either dexlansoprazole MR 60 or 90 mg [31]. Safety evaluations (AEs, changes in clinical parameters, laboratory results and gastric histology) were conducted at months 1, 3, 6, 9 and 12. Of the patients receiving dexlansoprazole MR 60 and 90 mg, 71 and 65%, respectively, experienced ≥1 treatment-emergent AEs, with the most frequent AE being upper respiratory infection (14 and 13% in the 60- and 90-mg groups). A total of 30 patients experienced ≥1 serious AEs but the majority were unrelated to study drug. No clinically meaningful or unexpected changes in any laboratory results were noted, nor were concerning gastric histologic changes seen. The authors concluded that 12-month treatment with dexlansoprazole MR 60 and 90 mg was well tolerated.

Regulatory affairs

Dexlansoprazole MR was approved for use in the USA in 2009, in Canada in 2010 and in Mexico in 2011. Dexlansoprazole MR is approved in the USA and Mexico for the healing of EE at a once-daily dose of 60 mg for up to 8 weeks, maintenance of healing of EE at a once-daily dose of 30 mg, and treating heartburn associated with nonerosive reflux disease at a once-daily dose of 30 mg for 4 weeks. In Canada, the dose and treatment duration for healing of EE and for treating heartburn associated with nonerosive GERD are the same as in the USA. However, for maintenance of healed EE, two doses were approved for use depending on the severity of initial mucosal injury (dexlansoprazole MR 30 mg was approved for maintenance of milder esophagitis and 60 mg for maintenance of more severe esophagitis).

Conclusion

Dexlansoprazole MR combines dexlansoprazole, the *R*-enantiomer of lansoprazole, with a dual delayed-release formulation to provide two distinct releases of drug after administration. This technology extends the effective plasma concentration and allows the drug to be taken without regard to food or timing of meals. Clinical trials confirm that dexlansoprazole MR taken once daily provides consistent healing of EE, maintains this healing and provides complete heartburn relief for most GERD patients. In studies conducted up to 1 year, dexlansoprazole MR appears to be well-tolerated with a safety profile comparable to lansoprazole.

Expert commentary

Proton pump inhibitors are the most effective and widely used treatment for GERD. Many PPIs are now available as generic or over-the-counter medications. Although these PPIs are generally successful in treating GERD symptoms, the extended pharmacokinetic and pharmacodynamic properties of dexlansoprazole MR may fill an unmet need for some patients. The longer duration of action of dexlansoprazole MR may be important for those individuals taking once-daily generic medication who still have residual or breakthrough symptoms later in the day or at night. A once-daily longer acting drug may be a more convenient alternative to twice-daily generic treatment. Certain patients (those with moderate-to-severe esophagitis, complicated GERD or Barrett's esophagus) who may require more aggressive acid control can benefit from dexlansoprazole MR with its more prolonged pharmacodynamic effect. Finally, those patients who find it difficult to comply with the meal-associated dosing required with other PPIs (e.g., those who eat at irregular times or late at night, shift workers, travelers) will likely benefit from the dosing flexibility of dexlansoprazole MR.

Five-year view

The prevalence of GERD will continue to increase in the USA and other Western countries as the population ages, becomes more overweight and embraces a less healthy diet and lifestyle. This increase will require addressing unmet needs of current treatments, particularly incomplete symptom relief, inadequate healing of moderate-to-severe esophagitis, and inconvenience of meal-associated dosing and short duration of action. Longer acting PPIs, such as dexlansoprazole MR, extended-release rabeprazole and new or modified PPIs under development with longer half-lives or enhanced action (ilaprazole, tenatoprazole, CAM-omeprazole, vecam [VB101]) [32], will assume a greater role, especially in cases where presumed acid-related symptoms are incompletely controlled with conventional generic medications or where appropriate dosing or compliance may be an issue.

Finally, endoscopic antireflux techniques and innovative surgical approaches, particularly natural orifice transluminal endoscopic surgery, may emerge as alternative to medical therapy of GERD for some individuals. This is especially true for those individuals suffering from regurgitation despite optimal medical therapy or those with severe esophagitis in whom control of esophageal reflux may prevent complications.

Financial & competing interests disclosure

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Key issues

- Conventional proton pump inhibitors (PPIs) do not control gastroesophageal reflux disease symptoms adequately in a significant proportion of patients. Improper meal-related PPI dosing is a common cause of breakthrough gastroesophageal reflux disease symptoms.
- Dexlansoprazole modified release (MR) is the only currently approved PPI that can be taken at any time of day without regard to meals.
- Short- and long-term safety data demonstrate dexlansoprazole MR to be well tolerated with a safety profile comparable to other PPIs.

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