


Effect of gastric acid-reducing agents on the pharmacokinetics and efficacy of lemborexant

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Abstract

Lemborexant is a dual orexin receptor antagonist approved for treating insomnia. As the solubility of lemborexant is pH-sensitive, the impact of the gastric acid-reducing agent (ARA), famotidine, on lemborexant pharmacokinetics was evaluated in a Phase 1 study. Additionally, post hoc analysis of data from Phase 3 studies examined the potential effect of concomitant ARAs on patient-reported/subjective sleep onset latency (sSOL) in subjects with insomnia. Coadministration of lemborexant 10 mg with famotidine decreased the maximum observed concentration by 27% and delayed time of maximum observed concentration by 0.5 hours. Famotidine did not affect overall lemborexant exposure based on comparison of area under the concentration curves. Concomitant ARA use in the Phase 3 studies did not impact the effect of lemborexant on sSOL; the change from baseline during the last 7 nights of 1 month of treatment with lemborexant 10 mg was -17.1 minutes with vs -17.9 minutes without ARAs. Collectively, these results indicate that lemborexant can be coadministered with ARAs.

KEYWORDS

gastric acid, insomnia, lemborexant, orexin receptor antagonists, pharmacokinetics

1 | INTRODUCTION

Insomnia is a common sleep disorder that can have a significant impact on health and quality of life.^{1,2} Lemborexant (E2006) is a novel, orally active dual orexin receptor antagonist³ that was recently approved by the US Food and Drug Administration and the Japanese Pharmaceuticals and Medical Devices Agency for the treatment of insomnia,⁴ and is under investigation for the treatment of other sleep disorders. Orexins are integral for the gating of wakefulness and in mediating the transition from sleep to wakefulness.

Dual orexin receptor antagonists act by blocking orexin receptors (orexin receptor 1 and orexin receptor 2 [OXR2]), thereby inhibiting the activity of orexin and the associated effects on sleep/wakefulness.⁵ As a reversible competitive antagonist, lemborexant binds rapidly to both orexin receptors, although with higher affinity for OXR2.⁶ In two pivotal Phase 3 clinical studies (Study E2006-G000-304 [Study 304; SUNRISE-1; NCT02783729] and Study E2006-G000-303 [Study 303; SUNRISE-2; NCT02952820]) in subjects with insomnia, lemborexant 5 mg and 10 mg significantly improved sleep onset and sleep maintenance compared with

The authors confirm that the Principal Investigator for this paper is Cynthia A. Zamora and that she had direct clinical responsibility for patients

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placebo at 1 month (Study 304) and through 12 months (Study 303), and was well tolerated.^{7,8}

Lemborexant is a Biopharmaceutics Classification System Class II molecule and exhibits pH-dependent solubility. Specifically, in vitro dissolution studies have shown that lemborexant exhibits delayed dissolution in weak acid and neutral conditions compared with dissolution at lower pH (Figure S1). Although the rate of dissolution is delayed, essentially complete release (approximately 90% or more) is achieved within 120 minutes for all four pH conditions evaluated (pH 3.0, 4.5, 6.8, and at 0.1 mol/L HCl [approximately pH 1]). These in vitro findings suggest that gastric acid-reducing agents (ARAs), which are commonly used to treat conditions such as gastroesophageal reflux disease, have the potential to delay or slow the rate of lemborexant absorption and thereby impact the effect of lemborexant to decrease the time to sleep onset.

Clinical studies have shown that lemborexant has a linear and predictable pharmacokinetic profile over a wide range of doses⁹; the approved therapeutic doses are 5 and 10 mg. The time to maximum plasma concentration (t_{max}) of lemborexant is approximately 1-3 hours.⁹ Lemborexant maximum plasma concentration (C_{max}) decreased by 23%, area under the concentration-time curve from time zero extrapolated to infinity ($AUC_{(0-inf)}$) increased by 18%, and t_{max} was delayed by 2 hours following administration of single-dose lemborexant 10 mg with a high-fat and high-calorie meal (unpublished data on file, Eisai Inc, Woodcliff Lake, NJ, USA). Lemborexant is mainly metabolized by cytochrome P450 3A (CYP3A),¹⁰ and drug-drug interaction study results indicate that concomitant use of lemborexant with strong or moderate CYP3A inducers and strong or moderate CYP3A inhibitors should be avoided (unpublished data on file, Eisai Inc, Woodcliff Lake, NJ, USA).

The objective of this Phase 1, single-center, open-label, fixed-sequence study was to examine the impact of the ARA, famotidine, on lemborexant pharmacokinetics. Famotidine was selected as it is a commonly used H₂ antagonist with established safety and pharmacokinetic profiles, characterized by a fast onset of effect and a lack of cumulative effects with repeat dosing. This fast onset of action makes famotidine an optimal choice for assessing potential gastric acid-modifying changes impacting sleep onset. After famotidine dosing is stopped, gastric pH returns to baseline within 10-12 hours. Famotidine is predominantly excreted in the urine unchanged and has a low potential for CYP-related drug-drug interactions.¹¹ Based on this information, famotidine was considered suitable for the single-dose study design. To explore the clinical relevance of any pharmacokinetic effect observed, a subsequent, post hoc analysis of pooled data from Study 304⁷ and Study 303⁸ was planned in the subpopulation of subjects taking concomitant ARAs (H₂ antagonists, proton pump inhibitors [PPIs], and/or antacids).

2 | METHODS

All clinical protocols were approved by relevant institutional review boards, and the studies were conducted in accordance

What is Already Known About this Subject

- Lemborexant is a dual orexin receptor antagonist approved for treating insomnia and being investigated as a treatment for irregular sleep-wake rhythm disorder.
- The solubility of lemborexant is pH dependent.

What this Study Adds

- Famotidine reduced lemborexant C_{max} by 27% and increased t_{max} , suggesting the potential to impact the time to sleep onset, but did not affect overall exposure.
- Using pooled retrospective data from Phase 3 studies, sleep latency following treatment in subjects with insomnia who were/were not taking concomitant acid-reducing agents (H₂ antagonists/proton pump inhibitors/antacids) was similar.
- These results indicate that lemborexant can be coadministered with gastric acid-reducing agents.

with the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice guidelines, and all applicable local regulations. All subjects provided written informed consent.

2.1 | Phase 1 study: effect of the H₂ antagonist famotidine on lemborexant pharmacokinetics

The effect of famotidine on lemborexant pharmacokinetics was examined in a Phase 1, open-label study (Study E2006-A001-012 [Study 012; NCT03451110]) in healthy adults ≥ 18 and ≤ 55 years of age. On Day 1 of the study, subjects received a single dose of lemborexant 10 mg in the morning after an overnight fast of ≥ 10 hours. Subsequently, on Day 15, subjects received a single dose of famotidine 40 mg in the morning after an overnight fast of ≥ 10 hours, followed by lemborexant 10 mg approximately 2 hours later.

Lemborexant concentrations were measured in blood samples collected predose and up to 216 hours postdose via a validated liquid chromatography with tandem mass spectrometry method. Pharmacokinetic parameters, including t_{max} , C_{max} , AUC from time zero to 72 hours postdose $AUC_{(0-72h)}$, AUC from time zero to time of last measurable concentration ($AUC_{(0-t)}$), and $AUC_{(0-inf)}$ were derived by noncompartmental analysis.

The effect of famotidine on the rate on lemborexant absorption was evaluated by comparing C_{max} and corresponding t_{max} values before and after famotidine administration.

Drug interaction assessment was based on the ratio of least squares geometric means (LSGMs) and corresponding 90% confidence intervals (CIs) for C_{max} and AUC for lemborexant on Days 1

and 15. The statistical assessment of famotidine coadministration with lemborexant was evaluated using repeated measures analysis of variance of log-transformed C_{max} and AUCs. Pharmacokinetic analyses were performed using Phoenix WinNonlin, version 6.3 (Certara, LP, Princeton, NJ, USA).

Safety assessments included monitoring and recording of all treatment-emergent adverse events (TEAEs), laboratory tests, vital signs, electrocardiograms, and physical examinations. Adverse events were coded per the Medical Dictionary for Regulatory Activities, version ≥ 20.1 .

2.2 | Phase 3 studies: Effect of ARAs (H_2 antagonists, PPIs, and/or antacids) on the efficacy of lemborexant

The effect of ARAs on the efficacy of lemborexant was examined in a post hoc analysis of pooled data from the Phase 3 Study 304 and Study 303. Study 304 was a 1-month, double-blind, randomized, placebo- and active-controlled, parallel-group study in 1006 male and female subjects with insomnia disorder ≥ 65 and ≥ 55 years of age, respectively. Subjects were randomized to placebo, lemborexant 5 mg, lemborexant 10 mg, or zolpidem tartrate extended release 6.25 mg. Study 303 was a 12-month (6-month placebo-controlled, 6-month active treatment), double-blind, randomized study in 949 male and female subjects with insomnia disorder ≥ 18 years of age. Subjects were randomized to placebo, lemborexant 5 mg, or lemborexant 10 mg. Both studies allowed for the use of ARAs (H_2 antagonists, PPIs, and/or antacids).

To assess the potential clinical relevance of the observed effect of famotidine to reduce and delay lemborexant C_{max} (see results section for further detail), a comparison of the effect of lemborexant on the pharmacologically relevant parameter subjective sleep onset latency (sSOL) in subjects using ARAs and not using ARAs on the days of PK sampling was undertaken. sSOL was compared between treatment groups across the first 7 nights and last 7 nights for subjects who were and were not using concomitant ARAs during 1 month of treatment. The parameter sSOL was selected as most sensitive to querying the potential clinical relevance of famotidine on the rate of lemborexant absorption.

The effect of ARA subgroups on the treatment ratio (active:placebo) was evaluated using a mixed-effect repeated measures analysis, with factors for study, ARA group, region, treatment, ARA-by-treatment interaction, and ARA-by-visit interaction as fixed effects, and baseline efficacy value as a covariate. The effects of ARAs on the treatment ratio within each ARA subgroup was evaluated using mixed-effect repeated measures analysis, with factors for study, age group, region, treatment, visit, and treatment-by-visit interaction as fixed effects, and baseline efficacy value as a covariate. Statistical comparisons for both of these models were carried out using LSGM for the treatment ratio on log-transformed data. Missing values were not imputed.

3 | RESULTS

3.1 | Phase 1 study: Effect of famotidine on lemborexant pharmacokinetics

In the Phase 1 study, 24 of 38 subjects passed screening. Of these subjects, 16 completed all assessments. Key demographics of the seven (43.8%) males and nine (56.3%) females who completed all assessments included a mean (standard deviation) age of 33.0 (7.0) years and body mass index of 25.1 (2.9) kg/m^2 .

Coadministration of lemborexant with famotidine decreased lemborexant median C_{max} by 27% and delayed median lemborexant t_{max} by 0.5 hours. There was no statistically significant effect on overall lemborexant exposure ($AUC_{(0-inf)}$; Table 1, Figure 1). LSGM ratios (90% CI) for lemborexant + famotidine/lemborexant alone were 73.2% (63.7-84.1) for C_{max} , 99.4 (91.1-108.5) for $AUC_{(0-t)}$, and 99.9 (91.7-108.8) for $AUC_{(0-inf)}$.

Of the 16 subjects completing the study, four (25.0%) experienced TEAEs; all were mild in severity. No TEAE was experienced by more than one subject. There were no serious adverse events, deaths, or discontinuations due to TEAEs. There were no clinically important changes in laboratory values, vital signs, electrocardiograms, or physical examination findings.

3.2 | Phase 3 studies: effect of ARAs on the efficacy of lemborexant

In Study 304 and Study 303, a total of 55 subjects in the placebo group, and 78 and 81 subjects in the lemborexant 5 and 10 mg groups, respectively, reported the use of at least one

TABLE 1 Lemborexant pharmacokinetic parameters after administration alone or in combination with famotidine

PK parameter	Geometric mean (CV%)	
	Day 1	Day 15
	LEM (n = 16)	LEM + FAM (n = 16)
t_{max} , h ^a	1.00 (0.50-4.00)	1.50 (1.00-4.00)
C_{max} , ng/mL	53.1 (52.5)	38.9 (36.0)
$AUC_{(0-72h)}$, ng·h/mL	317 (41.8)	309 (34.5)
$AUC_{(0-t)}$, ng·h/mL	402 (48.1)	400 (38.6)
$AUC_{(0-inf)}$, ng·h/mL	424 (50.7)	424 (41.5)

Note: $AUC_{(0-72h)}$, area under the concentration time curve from time zero to 72 hours postdose; $AUC_{(0-inf)}$, area under the concentration time curve from time zero extrapolated to infinity; $AUC_{(0-t)}$, area under the concentration \times time curve from time zero to time of last measurable concentration; C_{max} , maximum observed concentration; CV, coefficient of variation; FAM, famotidine 40 mg; LEM, lemborexant 10 mg; PK, pharmacokinetics; t_{max} , time of maximum observed concentration.

^a t_{max} data are median (range).

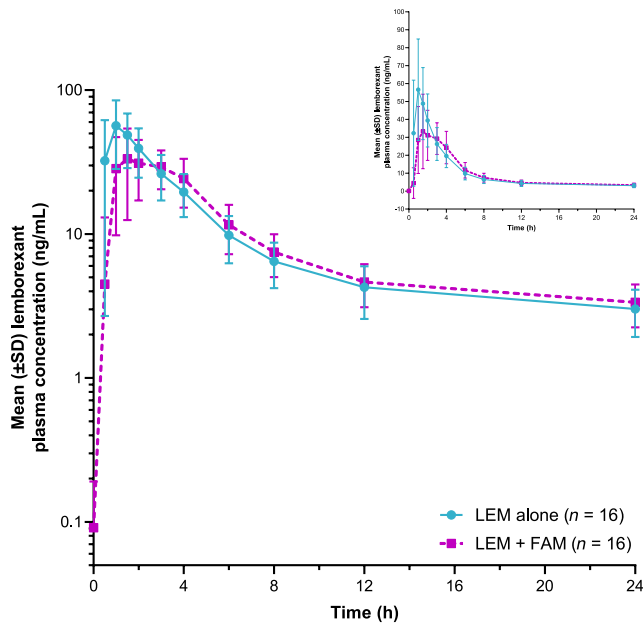


FIGURE 1 Plasma lemborexant concentration-time profiles for lemborexant alone (Day 1) and lemborexant coadministered with famotidine (Day 15). Main graph shows concentrations using a logarithmic scale; inset shows concentrations using a linear scale. Graphs are truncated at 24 hours postdose from the 216-hour time course. FAM, famotidine 40 mg; LEM, lemborexant 10 mg; SD, standard deviation

concomitant ARA. The mean duration of ARA use was as follows: placebo = 90.1 days for PPIs ($n = 42$), 60.5 days for H_2 antagonists ($n = 11$), and 13.8 days for antacids ($n = 5$); lemborexant 5 mg = 95.6 days for PPIs ($n = 60$), 73.2 days for H_2 antagonists ($n = 14$), and 64.1 days for antacids ($n = 8$); lemborexant 10 mg = 91.5 days for PPIs ($n = 63$), 54.6 days for H_2 antagonists ($n = 11$), and 89.2 days for antacids ($n = 10$).

Subgroup analyses of pooled data from Study 304 and Study 303 showed significant decreases from baseline ($P < .05$) in sSOL during the first 7 nights and the last 7 nights during 1 month of treatment for both lemborexant doses compared with placebo, regardless of whether subjects were or were not using concomitant ARAs (Figure 2). There was no significant effect of ARA use on the LSGM treatment ratio of the change from baseline in sSOL in either lemborexant treatment group during the first 7 nights or the last 7 nights during 1 month of treatment (all comparisons $P > .05$; Table S1).

4 | DISCUSSION

A key aim in the treatment of insomnia is to achieve a rapid onset of drug effect. The onset of drug effect is dependent on the rate and extent of drug absorption, which in turn depends on dissolution rate. Therefore, as the dissolution rate of lemborexant is pH dependent, as evidenced by a delay in dissolution rate with increasing pH, evaluating whether ARAs affect the pharmacokinetics of lemborexant is of clinical relevance. To this end, the analyses described in this manuscript

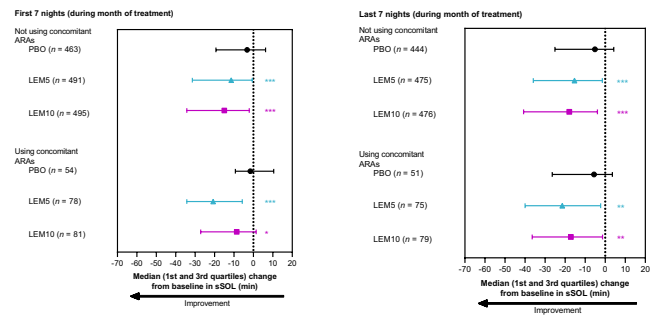


FIGURE 2 Effect of lemborexant on sSOL latency for the first 7 nights and the last 7 nights during 1 month of treatment in subjects with insomnia who were and were not using ARAs in Study 304 and Study 303. * $P < .05$; ** $P < .01$; *** $P < .0001$ vs PBO within each subgroup. Values are based on mixed-effect model repeated measurement analysis on log(sSOL) with factors of study, age group, region, treatment, visit, and treatment-by-visit interaction as fixed effects, and baseline log(sSOL) as a covariate. Missing values were not imputed and were assumed to be missing at random. ARA, gastric acid-reducing agent; LEM5, lemborexant 5 mg; LEM10, lemborexant 10 mg; PBO, placebo; sSOL, subjective sleep onset latency

examined the effect of ARAs (H_2 antagonists, PPIs, and/or antacids) on the pharmacokinetics of lemborexant. Consistent with in vitro findings, coadministration of famotidine resulted in a delay in lemborexant absorption (lower C_{max} and later t_{max}), suggesting the potential to affect the time to sleep onset, but had no impact on the extent of drug exposure (AUC). Availability of a large Phase 3 database (from Study 304 and Study 303) supported querying the potential clinical relevance of this pharmacokinetic effect by comparing a parameter (sSOL) potentially impacted by the rate of drug absorption. This post hoc analysis of Phase 3 data was conducted by comparing sSOL in subjects with insomnia who were and were not using concomitant ARAs (H_2 antagonists, PPIs, and/or antacids). As famotidine has a rapid onset of action, any effect on pH potentially impacting SOL would be similar to or greater than that for other gastric acid modifiers; hence, pooling of different ARAs in the post hoc analysis was considered appropriate. No significant effect of concomitant administration of ARAs on sSOL was observed. Taken together, the findings of these analyses indicate that although ARAs have a measurable effect (27% decrease in C_{max} and 0.5-hour delay in t_{max}) in slowing the rate of lemborexant absorption, this effect is not clinically relevant as evidenced by the lack of an effect on sSOL. These findings are also in keeping with those of a Phase 2 study of lemborexant, which demonstrated a relatively flat dose-response curve for sSOL for lemborexant doses ranging from 2.5 to 25 mg,¹² despite the fact that these doses are associated with marked differences in C_{max} .⁹ Further, given that C_{max} occurs approximately at 1 to 3 hours⁹ and that patients treated with lemborexant fall asleep well before this time,⁷ any slowing of absorption is unlikely to substantially impact sleep onset. Thus it can be concluded that coadministration of ARAs have no clinically meaningful effect on lemborexant pharmacokinetics.

Consistent with findings from other Phase 1 clinical studies⁹ and Studies 303 and 304,^{7,8} lemborexant was found to be well tolerated in the current Phase 1 study.

In conclusion, the results from these analyses indicate that lemborexant can be coadministered with ARAs (H₂ antagonists, PPIs, and antacids) and does not warrant dose modifications, which is supported by the lack of restrictive language in the US and Japanese prescribing information.

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CONFLICT OF INTEREST

All authors are employees of Eisai Inc or Eisai Co., Ltd.

AUTHOR CONTRIBUTIONS

All authors have: made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; been involved in drafting the manuscript or revising it critically for important intellectual content; given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

DATA SHARING STATEMENT

De-identified subject data that underlie the results reported in this article will not be made available, but summary information will be made available on ClinicalTrials.gov.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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