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Prescribing decisions should be made based on the approved package insert in the country of prescription.

Sponsor / Company: sanofi-aventis **Drug substance(s):** zolpidem	**Study Identifier:** NCT00630175 **Study code:** EFC5202
Title of the study: Evaluation of the hypnotic properties of zolpidem-MR 12.5 mg and zolpidem 10 mg marketed product compared to placebo in patients with primary insomnia. A double blind, randomized, placebo controlled, three way crossover study	
Study center(s): The study was conducted in 25 centers; 13 in the United States of America, 7 in Canada, and 5 in Australia.	
Study period: Date first patient enrolled: 22-Sept-2003 Date last patient completed: 24-Feb-2004	
Phase of development: Phase III	
Objectives: ▪ To evaluate the hypnotic efficacy of zolpidem-MR (modified release) 12.5 mg and zolpidem 10 mg marketed product in comparison with placebo in patients with primary insomnia and sleep maintenance difficulties, using polysomnography (PSG) recordings and patient sleep questionnaires; ▪ To evaluate the clinical safety and tolerability of zolpidem-MR 12.5 mg and zolpidem 10 mg marketed product in comparison with placebo.	
Methodology: International, multicenter, Phase 3b, randomized, placebo-controlled, three way crossover study in patients with primary insomnia and sleep maintenance difficulties.	
Number of patients: Planned: 108 Randomized: 114 Treated: 113 Evaluated: 106 for efficacy, 113 for safety	
Diagnosis and criteria for inclusion: ▪ male and female patients aged 18 to 64 years; ▪ diagnosis of primary insomnia based on Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria; ▪ sleep maintenance difficulties characterized by a mean PSG wake time after sleep onset (WASO) calculated on screening night (SN) 1 and SN2 nights ≥ 45 minutes, and no screening night with WASO < 30 minutes; ▪ total sleep time (TST) < 7 hours and > 3 hours (on both screening nights).	
Investigational product: zolpidem-MR (modified release) Dose: 12.5 mg Administration: Oral	
Duration of treatment: 2 nights per period (3 periods) **Duration of observation:** 24-26 days (3 periods of 2 consecutive nights separated by a 5-day washout period).	

Reference therapies: - zolpidem (Ambien®) Dose: 10 mg Administration: Oral
- placebo matching for zolpidem-MR Dose: not applicable Administration: Oral
- placebo matching for zolpidem Dose: not applicable Administration: Oral

Criteria for evaluation:

Efficacy:

- Hypnotic efficacy:

Primary endpoint: PSG WASO measured during the first 6 hours for each pair of nights.

Secondary endpoints:

- PSG: TST/sleep efficiency (SE); latency to persistent sleep (LPS); WASO per group of hours (hours 1 + 2 + 3; hours 4 + 5 + 6 and hours 7 + 8); WASO 1 to 8 hours; total number of awakenings;
- patient's sleep questionnaire: subjective WASO, TST, sleep onset latency (SOL), number of awakenings, quality of sleep, refreshing quality of sleep;
- patient's global impression (PGI);
- relative degree of satisfaction with the different study drugs.

- Other evaluation criteria: Sleep architecture.

Safety: Vital signs, physical examination, adverse events (AEs).

Statistical methods:

The primary analysis was based on the efficacy population taking into account all patients who were randomized, took at least 1 dose of double-blind study medication, provided at least 1 postbaseline efficacy datum in each period, were not discontinued and with no major dispensing error.

Efficacy

The primary efficacy variable was the mean change on PSG WASO during the first 6 hours of the night calculated on the mean of the 2 treated nights.

Analyses of efficacy parameters (except for PGI scale and satisfaction questionnaire) consisted of the comparison against placebo of the 2 zolpidem groups applying linear mixed effects models with fixed terms for sequence, period, treatment, with and without carry-over term, and random term for patient within sequence, using Statistical Analysis Software (SAS) proc mixed procedure.
Pairwise comparisons versus placebo were performed using linear contrasts by Dunnett's procedure. Estimate and 95% confidence intervals (CIs) for difference between active treatments and placebo were calculated within the mixed model framework.
Each item of the PGI scale was analyzed using logistic regression with terms for treatment, period, sequence and patient (sequence). Satisfaction questionnaire was summarized by sequence and globally, and a summary of treatment period answers was performed.

Safety

The analysis was based on the exposed population (all patients who were randomized and took at least 1 dose of double-blind study medication).
Treatment emergent adverse events (TEAEs) were summarized by primary system organ class (SOC) and preferred term [Medical Dictionary for Regulatory Activities (MedDRA)];

Vital signs: the analysis of individual abnormalities was based on internal version of potentially clinically significant abnormalities (PCSAs). Vital signs were also summarized using mean, standard deviation (SD), median, minimum and maximum.

Summary:

Subject disposition and baseline characteristics:

The majority of the exposed population was female (63.7%). The mean age (± SD) for the combined study groups was 43.7 ± 12.8 years, ranging from 18 to 62 years. The mean duration of the current episode of insomnia was 116.7 ± 113.0 months, ranging from 5 to 490 months. Twenty-seven patients (23.9%) reported having taken a sleep medication within 3 months prior to study entry.

The baseline characteristics of the study population for the main PSG parameters showed a mean TST of 362:03 ± 42:43 min:sec, a mean WASO 1 to 6 hours of 48:53 ± 29:06 min:sec, a mean WASO 1 to 8 hours of 80:04 ± 36:58 min:sec, a mean LPS of 43:31 ± 34:22 min:sec and a mean number of awakenings of 9.1 ± 3.5.

Efficacy results:

Primary endpoint

Polysomnography recordings of the 2 treated nights showed that mean PSG WASO (1 to 6 hours) was 22:57 min:sec shorter in the zolpidem MR 12.5 mg group in comparison with placebo while 18:57 min:sec shorter in the zolpidem 10 mg group in comparison with placebo. The difference between each active treatment group and placebo was statistically significant ($p<0.0001$).

Secondary endpoints

The per hour analysis of the effect of study treatment on PSG WASO showed that the effect of zolpidem-MR 12.5 mg was significantly greater than placebo from hour 1 up to hour 6 while the effect of zolpidem 10 mg was significantly greater than placebo from hour 1 up to hour 5.

Regarding the other PSG sleep parameters (SE, LPS and number of awakenings), both zolpidem treatment groups were significantly superior to placebo.

When measured subjectively on patient's questionnaire, the effects of both zolpidem treatments were significantly superior to those of placebo for the following criteria (WASO, TST, SOL, quality of sleep, number of nocturnal awakenings, refreshing quality of sleep, PGI items 1, 2 and 3). For PGI item 4 (study medication strength), only zolpidem-MR 12.5 mg was significantly greater than placebo.

Results of the questionnaire of satisfaction showed that, among the 3 treatment groups, zolpidem MR 12.5 mg was perceived to be the most effective for all sleep parameters (WASO, TST, number of nocturnal awakenings and quality of sleep) except for SOL. Zolpidem 10 mg treatment was perceived to be the most effective for the SOL parameter.

Safety results:

The percentage of patients who experienced at least 1 TEAE was similar in both zolpidem treatment groups (25.9% for zolpidem MR 12.5 mg and 24.1% for zolpidem 10 mg) and greater than in the placebo group (16.2%).

The most frequently reported TEAEs (≥5%) in the zolpidem MR 12.5 mg group were somnolence [7/112 patients (6.3%) versus 2/111 patients (1.8%) in the placebo group] and headache [6/112 patients (5.4%) versus 6/111 patients (5.4%) in the placebo group]. Likewise, the most frequently reported TEAEs in the zolpidem 10 mg group were also somnolence and headache [6/108 patients (5.6%) each].

There were no deaths or serious adverse events (SAEs) during the study period. One patient withdrew from the study due to confusional state after the second intake of zolpidem MR 12.5 mg.

No clinically relevant changes were observed in vital signs.

Issue date: 14-March-2008