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

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| **Sponsor / Company:** sanofi-aventis<br>**Drug substance(s):** zolpidem | **Study Identifier:** NCT00425243<br>**Study code:** LTE5407 (ZOLONG) |
| **Title of the study:** Evaluation of the long term efficacy and safety of zolpidem-MR 12.5 mg compared to placebo, when both are administered over a long term period "as needed", in patients with chronic primary insomnia | |
| **Study center(s):** Sixty-seven sites located in the United States | |
| **Study period:**<br>Date first patient enrolled: 31-aug-2004<br>Date last patient completed: 06-jan-2006 | |
| **Phase of development:** Phase III | |
| **Objectives:**<br>Primary: The primary objective of the study was to evaluate the hypnotic efficacy of zolpidem-MR 12.5 mg in comparison with placebo, when administered over a long term period, on an "as needed" basis, in patients with chronic primary insomnia.<br>Secondary: The secondary objectives of the study were as follows:<br>▪ evaluate the drug taking behavior over a long-term period;<br>▪ evaluate the clinical safety and tolerability of zolpidem-MR 12.5 mg in comparison to placebo administered over a long term period, on an as needed basis;<br>▪ evaluate potential rebound and withdrawal effects after discontinuation of a chronic as needed administration of zolpidem-MR 12.5 mg in comparison to placebo; | |
| **Methodology:** A national (US), multicenter, Phase 3b, randomized, double blind, placebo controlled, two parallel group study. | |
| **Number of patients :** Planned: 1000 Randomized: 1025 Treated: 1018 Efficacy: 1016 Safety: 1018 | |
| **Diagnosis and criteria for inclusion:**<br>▪ male and female patients with chronic primary insomnia, ages 18 through 64 years;<br>▪ written, signed, and dated informed consent. | |
| **Investigational product:** zolpidem-MR 12.5-mg tablet (an extended release form of zolpidem)<br>Dose: 12.5-mg Administration: Oral | |
| **Duration of treatment:** 24 weeks<br>**Duration of observation:** 26 weeks | |

**Reference therapy:** Placebo tablet identical to zolpidem-MR 12.5 mg tablet
Dose: not applicable Administration: Oral

**Criteria for evaluation:**

Efficacy:

Primary efficacy variable*:*

The primary efficacy variable was Item 1 (which assessed sleep aid) of the Patient Global Impression (PGI) scale. Item 1 consisted of the following 3 ordered categories:"helped me sleep", "did not affect my sleep", and "worsened my sleep".

Secondary efficacy variables*:*

The main secondary efficacy variables assessed "hypnotic efficacy" and were the following:

- Clinical Global Impression (CGI) – Improvement item (CGI-I);
- PGI (Items 2, 3, and 4, respectively, sleep induction, sleep duration, and medication strength);
- total sleep time (TST), from the Patient's Morning Questionnaire (PMQ);
- wake time after sleep onset (WASO) from the PMQ;
- sleep onset latency (SOL) from the PMQ;
- quality of sleep (QOS) from the PMQ;
- number of awakenings (NAW) from the PMQ.

Safety:

Safety was assessed through the use of reports of adverse events (AEs) and vital signs, ie, heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), weight, and body mass index (BMI).
Other safety parameters assessed were as follows: rebound effect: from the WASO and TST; withdrawal effect: from the Physician Withdrawal Checklist (PWC); pregnancy test; physical examination.

**Statistical methods:**

Efficacy:

Analyses concerning the primary variable PGI Item-1 "aid to sleep" and the main secondary variables related to CGI-I and to PGI Items 2, 3, and 4 were based on the data observed "at Week 12" in the intent-to-treat (ITT) population, using the following rules for missing data replacement: if data at Week 12 were missing, nonmissing data at Week 16 was to be used, otherwise, nonmissing data at Week 8 was to be used. No other replacement was performed.

Comparison between placebo and zolpidem-MR 12.5 mg for CGI I and PGI-Items 1, 2, and 3 was performed using a Cochran-Mantel-Haenszel test with rank score. Patient's global impression Item 4 "medication strength" was analyzed by using a Chi square test on "favorable" response.

Analysis of mean change from baseline for each PMQ derived parameter (TST, WASO, SOL, QOS, and NAW averaged over Week 9 to Week 12 was performed with an analysis of covariance (ANCOVA), using as fixed factor the treatment group and as covariate the baseline value centered on the grand mean (ie, subtracting the overall baseline mean value of the population). A similar rule for missing data replacement as the one used for the PGI and the CGI-I items was applied for PMQ parameters.

Safety:

Safety data were summarized by treatment group using descriptive statistics. Adverse events were coded using the Medical Dictionary of Regulatory Activities (MedDRA, Version 9.0) and were classified according to chronological criteria. The Sponsor defined the thresholds for potentially clinically significant abnormalities (PCSAs) of vital signs. Analyses of rebound effects during the randomized phase, which may be specified on nights off-treatment, and the post-treatment phase were also performed. All analyses were based on the treated population.

**Summary:**

**Subject disposition and baseline characteristics**:

A total of 1025 patients were randomized to treatment (1000 patients had been planned for). Of these 1025 patients, 1018 patients (349 in the placebo group and 669 in the zolpidem-MR 12.5 mg group) were exposed at least once to study treatment.

Of these 1018 patients, 405 (39.8%) withdrew from the study: 167 (47.9%) in the placebo group and 238 (35.6%) in the zolpidem-MR 12.5 mg group. The main reason for discontinuation was "lack of efficacy" in the placebo group [82 (23.4%) patients] and "subject's request" in the zolpidem-MR 12.5 mg group [63 (9.3%) patients].

The majority of the treated population was female (61.2%). Mean age (±SD) for the whole population was 45.7 ± 11.0 years, ranging from 18 to 64 years. A total of 662 subjects were Caucasian, 183 were Black, 14 were Asian, and 159 were classified as "Other". For the majority of patients, insomnia was diagnosed more than 5 years before the study.

A total of 187 (18.4%) patients declared having taken a sleep medication within 3 months before study entry.

Baseline characteristics (mean ± SD) of PMQ parameters were the following:

- TST = 294.8 ± 48.2 minutes;
- WASO = 100.6 ± 49.3 minutes;
- SOL = 75.7 ± 47.8 minutes;
- NAW = 3.1 ± 6.5.

Treatment groups were comparable at baseline for these sleep parameters.

The overall mean numbers of days with investigational product (IP) during the study were 86.3 and 112.2 for the placebo and zolpidem-MR 12.5 mg treatment groups, respectively. During each actual month of treatment, the mean number of days with IP was less in the placebo group compared with the zolpidem-MR 12.5 mg group.

**Efficacy results:**

Primary endpoint***:***

Zolpidem-MR 12.5 mg was significantly superior to placebo ($p<0.0001$) regarding the aid to sleep (PGI-Item 1) when both IPs were administered on an as needed basis for 3 months (endpoint at week 12). Some 89.8% of patients from the zolpidem-MR 12.5 mg group versus 51.4% of patients from the placebo group declared that the medication helped them sleep.

Secondary criteria***:***

Zolpidem-MR 12.5 mg as needed was also significantly superior to placebo as needed ($p<0.0001$) regarding aid to sleep (PGI-Item 1) from Week 4 to Week 24. The percentage of patients who considered that zolpidem-MR 12.5 mg as needed helped them sleep was stable over time (from 85.7% at Week 4 to 92.3% at Week 24). The percentage of patients who considered that placebo as needed helped them sleep increased over time (from 37.6% at Week 4 to 59.7% at Week 24).

Zolpidem-MR 12.5 mg was also significantly superior to placebo regarding time to fall asleep (PGI-Item 2), total amount of sleep (PGI-Item 3) and medication strength (PGI-Item 4), up to 6 months of treatment as needed. Percentages for the zolpidem MR 12.5 mg group were as follows:

- PGI Item 2: 69.4% at Week 4 and 77.9% at Week 24;
- PGI Item 3: 79.6% at Week 4 and 86.8% at Week 24;
- PGI Item 4: 65.3% at Week 4 and 75.2% at Week 24.

Percentages for the placebo group were as follows:

- PGI Item 2: 30.3% at Week 4 and 49.5% at Week 24;
- PGI Item 3: 36.1% at Week 4 and 54.8% at Week 24;
- PGI Item 4: 28.7% at Week 4 and 51.1% at Week 24.

**Efficacy results (cont'd)**:

On the PMQ, patients reported that zolpidem-MR 12.5 mg was significantly superior to placebo on the main sleep parameters (TST, WASO, and SOL) but also on the QOS up to 6 months, after an as needed administration.
When only nights with IP intake were considered, zolpidem-MR 12.5 mg was significantly and steadily superior to placebo for all PMQ sleep parameters (TST, WASO, SOL, NAW, and QOS), at each timepoint from Month 1 to Month 6.
For nights without IP intake, treatment groups were significantly different for all PMQ sleep parameters at almost all timepoints, with less improvement in the zolpidem-MR 12.5 mg group compared with the placebo group.

**Safety results**:

Overall, the percentage of patients with at least one treatment-emergent AE (TEAE) was greater in the zolpidem-MR 12.5-mg group (63.2%) than in the placebo group (51.3%). TEAEs that had a numerically greater incidence than in the placebo group, by decreasing order of frequency within the zolpidem-MR group were: headache, anxiety, somnolence, dizziness, fatigue, disturbance in attention, irritability, nausea, sinusitis, back pain, asthenia, and hypertension.
The incidence of AEs that lead to patient withdrawal from the study was greater in the zolpidem-MR 12.5 mg group (55 patients, 8.5%) compared with the placebo group (16 patients, 4.6%), mainly because of psychiatric and nervous system disorders.
There was one death in a 52-year-old male patient with a history of arterial hypertension and hypercholesterolemia randomized into the zolpidem-MR 12.5mg group, lost to follow-up on Day 3 and found dead at home on Day 20. It was not considered as related to study treatment by the Investigator.
Three placebo-treated patients and 15 zolpidem-MR 12.5 mg treated patients experienced Serious AEs (SAEs) that were treatment emergent; none were considered to be related to IP by the Investigators.
Treatment-emergent SAEs that were experienced by patients in the zolpidem MR 12.5 mg group (none were reported more than once) were: anxiety, appendicitis, perforated appendicitis, bladder cancer, bronchitis, chronic cholestycitis, food poisoning, alcoholic gastritis, gastrointestinal hemorrhage, hepatic enzyme increased, herpes zoster, hypertension, hyperglycemia (headache secondary to the hyperglycemia), myocardial infarction, nephrolithiasis, retroperitoneal hemorrhage, traumatic hematoma, and traumatic intracranial hemorrhage.
Treatment-emergent SAEs that were experienced by patients in the placebo group (none were reported more than once) were: angina pectoris, coronary artery disease, depression, and stent occlusion.
Minor and clinically nonrelevant changes of vital signs were observed.

When measured during the treatment period, on nights without treatment, no rebound effect was observed for WASO and TST, except during the first month. When assessed after final treatment discontinuation, no rebound effect was observed.

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