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Sponsor/Company: sanofi-aventis **Drug substance**: SR46349 (eplivanserin)	**Study Identifier**: NCT00253903 **Study code**: LTE6262

Title of the study:

Efficacy and safety of eplivanserin 5 mg/day on sleep maintenance insomnia: a 12-week multicenter, randomized, double-blind, placebo-controlled study followed by an open label extension phase with eplivanserin for 40-week period.

Study center(s):

International, multicenter study with 165 centers 14 countries

Study period:

Date first subject/patient enrolled:	11-Nov-2005
Date last subject/patient completed:	22-Nov-2007 (double-blind period) 10-Sep-2008 (open-label period)

Phase of development: 3

Objectives:

Double-blind treatment period (12 weeks)

The primary objective of this study was to assess efficacy of eplivanserin 5 mg/day in comparison to placebo after 12 weeks of treatment on sleep maintenance insomnia using patient sleep questionnaire, patient reported wake time after sleep onset (pr-WASO).

The main secondary objective of this study was to evaluate patient's daytime functioning using the Functional Outcomes of Sleep Questionnaire (FOSQ) Items 1 and 2 (concentration/memory) and Items 4 and 10 (hobby/work) with eplivanserin 5 mg/day as compared to placebo after 12 weeks of treatment.

Other secondary objectives were to evaluate residual effects (using patient's morning questionnaire) that may be associated with eplivanserin 5 mg/day as compared to placebo during double-blind treatment period (after each night of treatment), to evaluate the clinical safety of eplivanserin 5 mg/day compared to placebo after 6 and 12 weeks of treatment, and Health Outcomes: to assess the effect on patient's ability to work using the work limitation questionnaire (WLQ)

Open-label period (40 weeks)

Patients who completed the 12-week double-blind treatment period were proposed to participate in the open label period with eplivanserin 5 mg for an additional 40 weeks to evaluate patient's daytime functioning using the FOSQ with eplivanserin 5 mg/day, to evaluate the long-term clinical safety of eplivanserin 5 mg/day, and to assess the effect on sleep following abrupt discontinuation of eplivanserin 5 mg/day (during run-out period). The health outcome was to evaluate the effect on patient's ability to work using the WLQ.

Methodology:

Multicenter, randomized, double-blind, placebo-controlled study with 2 parallel groups of patients with sleep maintenance insomnia (SMI) followed by a 40-week open label period in patients who have completed the double-blind treatment period.

Number of subjects/patients:

Planned:	1120
Randomized:	1155
Treated:	1145 in double-blind period, 911 in open-label period (673 completers from eplivanserin group and 238 completers from placebo group of the double-blind period)
Efficacy population:	1145 in in double-blind period, 911 in open-label period
Safety population:	1145 in all double-blind treated population, 911 in all open label treated population, and 1088 in all eplivanserin-treated population

Diagnosis and criteria for inclusion:

Out-patients ≥18 years of age with the diagnosis of primary insomnia based on diagnostic and statistical manual of mental disorders-fourth edition (DSM-IV) criteria with predominant complaints of difficulty of initiating or maintaining sleep (nocturnal awakenings), or nonrestorative sleep for at least 1 month preceding the study visit.

Disturbances of sleep maintenance based on patient' s information were:

- patient has spent at least 6.5 hours and no more than 9.0 hours in bed each night over the preceding 2 weeks
- patient must complain of at least 1 hour of wake time after sleep onset (WASO) for at least 3 nights per week over the preceding month
- patient must report impact on daytime functioning associated with sleep maintenance insomnia as measured by Item 3 of insomnia severity index (ISI) at screening and randomization visits.

Based on the information recorded in the patient's diary during the screening week preceding the randomization:

- mean pr-WASO per night ≥60 min during screening period (7 days) and no period of pr-WASO <45 min on each screening night (2 nights with pr-WASO <45 min during screening period were acceptable. In addition, 2 lowest pr-WASO values were to be excluded from the calculation of the mean pr-WASO.
- Total sleep time (TST) ≤7 hours and ≥3 hours on 3-worst screening nights.

Mean patient reported sleep onset latency (pr-SOL) per night had to be ≤30 min during the screening period. One highest SOL value was to be excluded from the calculation of mean SOL.

Investigational product: SR46349 (eplivanserin)

Dose: 5 mg/day

Administration: 1 tablet orally at dinner time during each treatment period

Reference therapy: Placebo tablets

Administration: 1 tablet orally at dinner time during each treatment period

Duration of treatment: 12 weeks double-blind period and 40 weeks open label treatment period

Duration of observation: 55 weeks

Criteria for evaluation:

Efficacy:

Primary endpoint

The primary endpoint was the change from baseline at Week 12 of the mean pr-WASO measured by Item 5 of the patient's sleep questionnaire.

Main secondary endpoint

Main secondary endpoint was the change from baseline at Week 12 of the FOSQ mean of Items 1 and 2 (concentration/memory) and mean of Items 4 and 10 (hobby/work).

Other secondary endpoints

Other secondary endpoints were daily assessments from patient's morning questionnaire, the change from baseline at

Week 6 and Week 12 of the following parameters: patient reported WASO (pr-WASO) at Week 6 only, patient reported number of nocturnal awakenings (pr-NAW), measured by Item 4 of the patient's sleep questionnaire, patient reported total sleep time (pr-TST), measured by Item 6 of the patient's sleep questionnaire, patient reported sleep onset latency (pr-SOL), measured by Item 3 of the patient's sleep questionnaire, and patient reported sleep quality and refreshing sleep quality, measured by Item 8 and 9 of the patient's sleep questionnaire.

Additional other secondary efficacy variables made at each visit, were the change from baseline at Week 6 and Week 12 of the following parameters: sub-score for each domains (general productivity, activity level, vigilance, intimacy and sexual relationship, social outcome) and total score of the FOSQ, mean of Items 1 and 2 and 4 and 10 of the FOSQ at Week 6 only, total score for anxiety and for depression of the hospital anxiety and depression scale (HADS), and patient global impression (PGI) rated by the patient at Week 6 and Week 12.

Health economics were the scores of the Work Limitation Questionnaire (WLQ) (ie, WLQ scale score and WLQ productivity loss score at Week 6 and Week 12).

Safety:

Safety assessments included the occurrence of treatment emergent adverse events (TEAEs), laboratory evaluations, vital signs, electrocardiograms (ECGs), next day residual, rebound, and withdrawal effects.

Statistical methods:

Double-blind treatment period (12 weeks)

Efficacy:

Primary endpoint

Main analysis

As primary analysis, the comparison of the pr-WASO (change from baseline) between eplivanserin versus placebo was performed at Week 12 on intent-to-treat (ITT) population, with a mixed-effect model with repeated measures (MMRM) approach, assuming the missing at random. This model was run using the statistical analysis software (SAS) mixed procedure with an unstructured correlation matrix to model the within-patient errors. Parameters were estimated using restricted maximum likelihood method with the Newton-Raphson algorithm. Denominator degrees of freedom were estimated using Satterthwaite's approximation.

This model included the fixed effects categorical effects of treatment, visit, and treatment-by-visit interaction, as well as the centered baseline mean pr-WASO (ie, baseline mean pr-WASO after centered baseline individual values on the grand mean baseline) as continuous fixed covariate. This model provided the baseline adjusted least-squares means (LS-means) estimates at Week 12 by treatment group, as well as the difference of these estimates versus placebo, with their corresponding standard errors, degrees of freedom, Student's t-test statistics and associated 95% confidence interval (CI).

Supportive analysis

To assess the sensitivity of the primary analysis, supportive analyses of covariance (ANCOVA) were performed based on "Last observation carried forward (LOCF)" and "Observed cases (OC)".

Main secondary endpoints

The main secondary endpoints were analyzed using exactly the same model (MMRM on ITT population) as for primary analysis.

Other secondary endpoints

The mean change from baseline at Week 6 and Week 12 of other patient's morning sleep questionnaire variables, the change from baseline of total subscore of the HADS, and FOSQ mean of Items 1 and 2 (concentration/memory) and Items 4 and 10 (hobby/work) at Week 6 only, and total scores for the domains of the FOSQ (general productivity, activity level, vigilance, intimacy and sexual relationships, social outcome, and total score) were analyzed using the same model as for the primary and main secondary analyses (MMRM).

For the PGI scales, percentages for each category were described by group at each evaluation under double-blind period (by visit using OC strategy). Analyses were performed using Chi square test to compare percentages of favorable responses at the end of double-blind treatment (for each of the 4 questions) versus unfavorable ones.

For health economic variables, the change from baseline at Week 6 (Visit 5) and at Week 12 (Visit 7) were carried out with ANCOVA (LOCF strategy) using the treatment group as fixed-effect and the centered baseline value as covariate.

Safety:

Adverse events

Treatment-emergent adverse events (TEAEs) were defined as adverse events (AEs) that developed, worsened or became serious during the on-treatment period. The TEAE definition during the double-blind period did not include the additional 14 days (5 half-lives) after the last study drug intake unless the patient discontinued the double-blind treatment. However, if the open label period started more than 1 day after the end of the double-blind period, the TEAE definition included all AEs starting or worsening up to the minimum between the start date of the extension and the stop date of the double-blind + 14 days (5 half-lives). Events occurring the day of the first double-blind intake were considered as TEAEs.

For summaries of all TEAEs, serious adverse events (SAEs), and AEs leading to treatment discontinuation, counts were provided by-treatment group for each preferred term within each system organ class concerned. Percentages were calculated with the number of patients from the exposed population in each group.

Laboratory, vital signs, and ECG parameters

Summaries of patients having at least 1 treatment-emergent potentially clinically significant abnormality (PCSA) for laboratory, ECG, and vital signs parameters were provided taking into account any abnormalities during treatment period.

Next day residual effects

The next day residual effects assessed in the sleep morning questionnaire (sleepiness in the morning and ability to concentrate in the morning) were analyzed similarly as the secondary endpoints at Week 12 and through the change versus baseline using MMRM analysis.

Rebound insomnia

Rebound insomnia was assessed through the pr-WASO and pr-TST during the run-out period: for each week and for the mean of the 14-day run-out period, the change from baseline was analyzed with ANCOVA adjusted for the baseline value.

Withdrawal effects

Withdrawal effects were assessed through the total score of the physician withdrawal checklist (PWC). The change from the end of study treatment to each week of the run-out period was analyzed with ANCOVA with the end of treatment value as covariate.

Analyses of the open label period data

The following populations were considered for the analyses: all open label treated population included all randomized patients who took at least 1 dose of the double-blind study medication and who were treated during the open label period; all eplivanserin-treated population included all patients who took at least 1 dose of eplivanserin medication in the double-blind or open label period.

Efficacy:

Efficacy analysis was performed on all open label treated population displaying all visits (double-blind treatment period and open label treatment period). All patient-reported efficacy variables were averaged by period.

The mean change from baseline to theoretical visit time points of all patient's morning sleep questionnaire variables, the mean of the FOSQ Questions 1 & 2 (concentration/memory) and 4 & 10 (work/hobby), and scores for the FOSQ domains and the change from baseline of total subscores for HADs were analyzed using MMRM analysis. As in the double-blind period, the model included fixed categorical effects of treatment, visit and treatment-by-visit interaction as well as the centered baseline as continuous fixed covariate. For the PGI scales, percentages for each category were described by group at each evaluation under double-blind and open label period (by visit using OC strategy).

For health economy variables, additionnal analyses (including open label period) were performed. The mean change from baseline to each theoritical visit time points were analyzed using MMRM model on the all treated open label population. Same MMRM model as for the other efficacy parameters was used.

Safety:

Analyses of AEs were performed by cumulative periods under eplivanserin exposure (the cumulative analysis was computed on all eplivanserin-treated population using the timepoints such as: event ≤3 months exposure; event ≤6 months exposure; and all events); by duration of eplivanserin exposure (the actual eplivanserin exposure was computed on all eplivanserin-treated population ie, 0 to 3 months exposure, 3 to 6 months exposure, 6 to 12 months exposure, and more than 12 months exposure); by treatment group at cut-off dates of the open label period (the analysis of the open label period only was presented on all open

label treated population at four cut-off dates of 3, 6, 9 months, and overall open label period.
For summaries of all AEs (SAEs and AEs leading to discontinuation), counts were provided by treatment group at cut-off dates, by duration of eplivanserin exposure group, and by timepoints (event ≤3 months, event ≤6 months, and all events) for each preferred term within each SOC concerned. Percentages were calculated with the number of patients from the exposed population entered in the open label period by each treatment group, by each group of duration of eplivanserin exposure, and by the number of patients from the exposed eplivanserin population.

Laboratory, vital signs, and ECG parameters

The analyses of PCSAs were performed on all eplivanserin-treated population using the cumulative periods under eplivanserin exposure (event ≤3 months, event ≤6 months, and all events).

Summaries of patients having at least 1 eplivanserin-treatment emergent PCSA for laboratory, ECG, and vital signs parameters were provided taking into account any abnormalities during the treatment period.

Residual effects

The residual effects assessed from the sleep morning questionnaire (sleepiness in the morning and ability to concentrate in the morning) were analyzed like the other parameters of the morning questionnaire at each theoretical visit of the double-blind and open label periods through the change versus baseline using MMRM analysis.

Additional analyses not pre-defined in the SAP were added following the more complete analyses performed in the clinical summary of safety:
analyses of time to first onset for selected TEAEs during the double-blind period (TEAE with an incidence ≥1% and at least 1% higher than the placebo group) and to time to treatment discontinuation due to AE were performed using nonparametric approach. Kernel-smoothed estimators (smoothed by 28 days) of the hazard function based on Nelson-Aalen estimator were calculated and plotted for the overall study on the all eplivanserin treated population.
Summaries of incidence of patients having at least 1 potentially clinically significant abnormality (PCSA) under treatment or within 14 days after the end of treatment by interval of time of two months for laboratory and vital signs parameters or 4 months for EGC parameters (larger window because of less scheduled assessments) were provided for the all eplivanserin treated population.
Treatment difference and 95% confidence interval using the Wilson score method were added for PCSA incidence of vital sign parameters during double blind treatment period.
Additional analyses have been added for the elderly treated eplivanserin population to better summarize their profile for AEs and vital signs during the whole eplivanserin exposure.

Summary:

Population characteristics

All double-blind treated population

A total of 1155 patients in 14 countries were randomized. There were 9 randomized patients who did not receive any of the study treatment and 1 patient had an unknown status of exposure. Hence, 1145 patients received the treatment (295 patients received placebo and 850 patients received eplivanserin), which consisted of the all double-blind treated population and the ITT population of the double-blind period.

All open label treated population

Among the completers of the double-blind treatment period, a total of 911 patients were treated in the open label period (post-placebo 238 and post-eplivanserin 673), which consisted of the all open label treated population.

All eplivanserin-treated population

A total of 1088 patients were exposed to eplivanserin (inclusive of the double-blind period and open label period), which consisted of the all eplivanserin-treated population. The numbers of patients exposed to eplivanserin were 204 patients between 0 to 3 months, 187 patients between 3 to 6 months, 527 patients between 6 to 12 months, and 170 patients in ≥12 months.

Efficacy results:

Double-blind treatment period

Demographic and baseline efficacy characteristics

Baseline demographic and patients' characteristics were similar in both eplivanserin and placebo groups. Overall mean age was 51.9 years and 15.1% of the total treated patients were elderly (aged ≥65 years). The overall percentage of female patients was slightly higher (59.7%) than male patients (40.3%) in both treatment groups.

Insomnia characteristics at baseline were similar between treatment groups, with 36.5% of the all double-blind treated population diagnosed with insomnia for more than 10 years before randomization. The severity of insomnia at baseline was similar in both treatment groups.

Other baseline characteristics for sleep parameters were similar in both treatment groups. Overall mean wake time after sleep onset was about 2 hours and the mean total sleep time was about 5.5 hours.

More than one-third (44.9%) of the all double-blind treated population in both treatment groups have taken previous medications affecting sleep before the conduct of the study (ie, analgesics, hypnotics and sedatives, antihistamines for systemic use, and anxiolytics).

Primary efficacy endpoint

Analysis of the primary efficacy endpoint showed that eplivanserin 5 mg/day improved sleep maintenance by decreasing from baseline the patients' reported wake time after sleep onset (pr-WASO) by 53:17 ± 1:30 min:sec after 12 weeks of treatment. The difference versus placebo was -13:31 min:sec, p-value <0.0001).

Main secondary efficacy endpoints

The analysis of the change from baseline at Week 12 in the mean of the FOSQ Items 1 and 2 (concentration/memory) did not reach the statistical significance level at 5% (LS mean difference from placebo of 0.09 [95% CI: -0.00 to 0.18]). As this was a hierarchical step down procedure, further conclusions cannot be made on the significance of the other secondary variable, mean of Items 4 and 10 (hobby/work) (LS mean difference from placebo of 0.10 [95% CI: 0.02 to 0.19]).

Other secondary efficacy endpoints

Daily patient's morning questionnaire

The MMRM analyses of the change from baseline of the daily patients' morning questionnaire parameters showed the following:

- the wake time after sleep onset (pr-WASO) at Week 6 decreased (improved) more in the eplivanserin group compared with the placebo group (LS mean difference from placebo of -14:21 min:sec [95% CI: -20:01 to -8:40]); the total sleep time (pr-TST) at Week 6 and Week 12 increased more in the eplivanserin group compared to the placebo group (LS mean difference from placebo of 13:20 min:sec [95% CI: 6:52 to 19:49] at Week 6 and 16:20 min:sec [95% CI: 9:14 to 23:27] at Week 12);
- the number of nocturnal awakenings (pr-NAW) at Week 6 and Week 12 decreased (improved) in the eplivanserin group compared with the placebo group (LS mean difference from placebo of -0.34 [95% CI: -0.52 to -0.16] at Week 6 and -0.35 [95% CI: -0.50 to -0.19] at Week 12);
- the sleep quality scores at Week 6 and Week 12 decreased (improved) in the eplivanserin group compared with the placebo group (LS mean difference from placebo of -0.13 [95% CI: -0.20 to -0.05] at Week 6 and -0.14 [95% CI: -0.21 to -0.06] at Week 12);
- the sleep refreshing quality scores at Week 6 and Week 12 decreased (improved) in the eplivanserin group compared with the placebo group (LS mean difference from placebo of -0.13 [95% CI: -0.20 to -0.06] at Week 6 and -0.15 [95% CI: -0.23 to -0.07] at Week 12);
- the pr-SOL at Week 12 was not modified in both treatment groups.

Functional Outcomes of Sleep Questionnaire

Of the FOSQ parameters assessed in the study, the eplivanserin group showed slightly increases (improved) compared with the placebo group in the following:

- items 1 and 2 (concentration/memory) at Week 6 (LS mean difference from placebo of 0.10 [95% CI: 0.01 to 0.19]);
- general productivity score (LS mean difference from placebo of 0.06 [95% CI: 0.00 to 0.13] at Week 6 and 0.09 [95% CI: 0.02 to 0.15] at Week 12);
- core (LS mean difference from placebo of 0.06 [95% CI: 0.00 to 0.13] at Week 6 and 0.09 [95% CI: 0.02 to 0.15] at Week 12);
- activity level score (LS mean difference from placebo of 0.08 [95% CI: 0.01 to 0.15] at Week 6 and 0.09 [95% CI: 0.02 to 0.17] at Week 12);

- vigilance score (LS mean difference from placebo of 0.10 [95% CI: 0.02 to 0.18] at Week 6 and 0.15 [95% CI: 0.07 to 0.23] at Week 12);
- social outcome score (LS mean difference from placebo of 0.10 [95% CI: 0.02 to 0.19] at Week 12); and
- total score (LS mean difference from placebo of 0.36 [95% CI: 0.06 to 0.67] at Week 6 and 0.50 [95% CI: 0.17 to 0.83] at Week 12).

There was no apparent difference between the treatment groups in the FOSQ Items 4 and 10 (hobby/work) at Week 6, social outcome score at Week 6, and in intimacy and sexual relationship score at Week 6 and Week 12.

Patient global impression

The percentages of patients with favorable responses in the patients' global impression (PGI) scales were higher in the eplivanserin group compared with the placebo group at Week 6 and Week 12:

- item-1, aid to sleep: treatment has helped in 56.7% of patients in the eplivanserin group versus 42.7% in the placebo group at Week 6 (p-value <0.0001) and respectively in 54.5% versus 41.3% at Week 12 (p-value = 0.0004);
- item-2, sleep induction: treatment has shortened sleep induction in 24.7% of patients in the eplivanserin group versus 18.1% in the placebo group at Week 6 (p-value = 0.0285) and respectively in 29.1% versus 22.2% at Week 12 (p-value = 0.0349);
- item-3, sleep duration: treatment has lengthened sleep duration in 52.0% of patients in the eplivanserin group versus 41.5% in the placebo group at Week 6 (p-value = 0.0037) and respectively in 50.8% versus 38.3% at Week 12 (p-value 0.0007);
- item-4: medication strength: treatment was considered just right in 46.5% of patients in the eplivanserin group versus 30.4% in the placebo group at Week 6 (p-value <.0001), and respectively in 45.6% versus 29.6% at Week 12 (p-value <.0001).

Work limitations questionnaire (WLQ)

The analysis on health-related work productivity using the WLQ showed that at Week 6 and Week 12, eplivanserin 5 mg/day decreased (improved) the productivity loss score and in 3 out of 4 subscores related to time management, mental interpersonal, and output scales:

- productivity loss score LS mean from placebo of -0.005 (95% CI: -0.011 to 0.001) at Week 6 and -0.007 (95% CI: -0.013 to -0.001) at Week 12;
- time management score LS mean from placebo of -2.62 (95% CI: -5.44 to 0.20) at Week 6 and -3.44 (95% CI: -6.25 to -0.62) at Week 12;
- mental-interpersonal score LS mean from placebo of -3.32 (95% CI:-5.66 to -0.98) at Week 6 and -2.83 (95% CI: -5.26 to -0.40) at Week 12; and
- output score (LS mean from placebo of -2.10 (95% CI: -4.76 to 0.56) and -3.01 (95% CI: -5.72 to -0.31) at Week 12.

The WLQ physical score was not impacted at Week 6 and Week 12.

Open label treatment period

Long-term efficacy analysis showed that the decreases (improvement) in the mean of pr-WASO from baseline with eplivanserin 5 mg/day persisted after 12 weeks and up to 1 year of treatment. The decreases in patients who were previously from the eplivanserin group were stable over time up to 1 year of treatment (maximum LS mean change from baseline of -66:55 min:sec at 12 months). While patients who were previously from the placebo group and switched to eplivanserin 5 mg during the open label period showed marked decreases starting from Week 16 up to 1 year of treatment (maximum LS mean change from baseline of -60:38 min:sec at 12 months). During 9 months of open label period following the marked decrease at Week 16, post-placebo patients showed almost similar decreases with those observed with post-eplivanserin patients.

Work limitations analysis showed that the productivity loss score, mental interpersonal score, WLQ out put score, WLQ physical score and time management score decreased (improvement) from baseline during the OL period regardless of treatment received during the double blind period.

Safety results:

A total of 1145 patients were exposed for 12 weeks to the double-blind study drug (295 to placebo and 850 to eplivanserin). Of them 911 continued the open label treatment with eplivanserin up to 1 year.

In the eplivanserin group, the percentage of patients with insomnia who experienced at least 1 TEAE and those who discontinued the study treatment due to AEs in the double-blind phase was greater than in the placebo group (55.5% and 4.2% in eplivanserin group versus 50.5% and 2.4% respectively). The percentage of patients who experienced any serious TEAE was low and

comparable between groups (2.2% in eplivanserin vs. 2.0% in placebo). The most frequently reported TEAEs during the double-blind period (with a frequency of ≥1% and at least 1% higher than the placebo group) were: dizziness (4.8% vs. 3.4%), diarrhea (3.9% vs. 2.0%), somnolence (3.6% vs. 1.0%), dry mouth (3.6% vs. 1.7%), constipation (2.2% vs. 0.7%), diverticulitis (1.6% vs. 0%) and upper abdominal pain (1.2% vs 0%). Analysis by age showed that elderly eplivanserin treated patients reported more TEAEs than non-elderly patients (diverticulitis, nasopharyngitis and upper respiratory tract infection).

One year safety analysis in any eplivanserin treated patients showed that the 68.1% of patients had at least 1 TEAE and 9.8% discontinued due to TEAEs. Patients who experienced a serious TEAE up to 1 year (or more) represented 4.0% of the global eplivanserin treated population. Overall when taking into account the exposure of the patients, the incidence of any TEAE, SAE or AE leading to discontinuation did not increase with longer exposure to eplivanserin 5 mg up to 1 year.

A total of 18 patients (1.7%) experienced diverticulitis under entire eplivanserin exposure. Nine were elderly. Seven patients were male and 11 were female. Eleven of whom had a medical history of diverticulitis, diverticulosis or diverticular disease. Most of the events were of moderate intensity and 6 patients had serious episodes. Eight patients had more than one episode. Seventeen patients had corrective treatment. Of whom 15 patients received antibiotics, one patient underwent also surgery. One patient discontinued the treatment for endoscopy during an episode of divertivulitis. After the first 12 weeks of treatment the incidence of diverticulitis remained stable.

No unexpected findings with no trend of increased incidence with longer exposure to eplivanserin, was identified from both double-blind period and the whole eplivanserin treatment up to 1 year, in clinical laboratory parameters.

During the double blind period, the percentage of patients with at least 1 on-treatment PCSA in vital signs (supine heart rate, systolic blood pressure (SBP) and diastolic blood pressure (DBP); orthostatic hypotension and weight) were similar between treatment groups in the global safety population. However an age effect was observed in elderly patients for orthostatic hypotension, where 12.3% and 18.5% eplivanserin elderly patients had an orthostatic SBP and an orthostatic DBP respectively, versus 5.1% and 7.7% in placebo. No trend of increased incidence with longer exposure to eplivanserin was identified from the whole eplivanserin treatment up to 1 year, in vital signs parameters.

During the double blind period, the percentage of patients with at least 1 on-treatment PCSA in ECG parameters were comparable between treatment groups. Four patients with normal QTcF at baseline presented with isolated QTcF≥500 ms during the open label period. No trend of increased incidence in ECG abnormalities with longer exposure to eplivanserin was identified from long term safety data.

There was no evidence of next day residual effect during the double-blind and open label treatment periods. There was no evidence of rebound insomnia. There was no meaningful withdrawal effects during the run out period.

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