European Medicines Agency

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WITHDRAWAL ASSESSMENT REPORT
FOR
SLIWENS

International Nonproprietary Name: **Eplivanserin**

Procedure No. EMEA/H/C/1102

This Assessment Report is based on the latest assessment report adopted by the CHMP with all information of a commercially confidential nature deleted.

This should be read in conjunction with the "Question and Answer" document on the withdrawal of the application: the Assessment Report may not include all available information on the product if the CHMP assessment of the latest submitted information was still ongoing at the time of the withdrawal of the application.

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I.   RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the CHMP considers that the application for EPLIVANSERIN in the treatment of chronic insomnia characterized by difficulties with sleep maintenance as measured by duration and number of nocturnal awakenings is not approvable since major objections pertaining to the demonstration of efficacy and safety have been identified.

II.   EXECUTIVE SUMMARY

Insomnia is the most common sleep complaint across all stages of adulthood, and for millions, the problem is chronic. Insomnia often is comorbid with other disorders, particularly depression, as well as some cardiovascular, pulmonary, and gastrointestinal disorders. In the absence of comorbid conditions, insomnia is thought to be a primary disorder in itself. Whether it is the primary disorder or secondary to some other condition, chronic insomnia is often associated with a wide range of adverse conditions, including mood disturbances, difficulties with concentration, and memory. Whether insomnia is the cause or result of associated problems is not always easily determined, but is critical to treatment strategies for individual patients.

Insomnia may be defined as complaints of disturbed sleep in the presence of adequate opportunity and circumstance for sleep. The disturbance may consist of one or more of three features: (1) difficulty in initiating sleep; (2) difficulty in maintaining sleep; or (3) waking up too early. A fourth characteristic, nonrestorative or poor-quality sleep, is also part of the DSM-IV definition, although there is controversy as to whether individuals with this complaint share similar pathophysiologic mechanisms with the others.

Chronic insomnia should be distinguished from acute insomnia, which may occur in anyone at one time or another (e.g., the night before an important event the next day). While some papers have utilized 6-month duration of the above symptoms to define chronicity, there is evidence to suggest that as few as 30 days of symptoms are clinically important.

Current pharmacologic treatments for insomnia mainly involve GABAergic (γ- aminobutyric acid) mechanisms rather than affecting circadian rhythms. Most currently prescribed sleep agents are benzodiazepine receptor agonists (BZRAs), which induce sleep by binding to the benzodiazepine receptor site of the GABA-A receptor complex. GABA is the major inhibitory transmitter in the central nervous system (CNS), and its receptors are distributed widely throughout the brain. BZRAs can cause a wide range of ancillary effects not directly related to sleep, depending on the precise subset of GABA-A receptors activated. These include sedative, anxiolytic, muscle-relaxant, and amnesic effects. The risk of tolerance, paradoxical effects, dependence, and abuse associated with the BZRAs may also reflect effects of these drugs on the GABA-A receptor complex.

The intended indication for eplivanserin is: Sliwens is indicated for treatment of chronic insomnia characterized by difficulties with sleep maintenance as measured by duration and number of nocturnal awakenings.

Eplivanserin did not affect sleep onset in clinical studies, a finding consistent with its non-sedative pharmacological profile.

II.1   About the product

Eplivanserin (SR46349, Z/E isomer) is an orally active 5-hydroxytryptamine (5-HT, [serotonin]) subtype 2 (5-HT2) receptor antagonist with a high affinity for human cloned 5-HT subtype 2A (5-HT2A) receptors (IC50 = 0.89 nM) and a 10-fold lower affinity for human cloned 5-HT2C receptors (IC50 = 10 nM). Serotonin is a neurotransmitter that plays a major role in many physiological and behavioural functions involving the central nervous system (CNS) but also gastrointestinal, cardiovascular and other systems. The 5-HT2 receptor family has been associated with the regulation of numerous cerebral activities including sleep regulation (sleep-waking cycle). In animals, eplivanserin induced a dose-dependent increase in the mean duration of slow-wave sleep (SWS) episodes accompanied by a reduction of the mean number of SWS episodes. In electroencephalogram (EEG) studies in healthy subjects, single oral doses (1, 10, and 40 mg) of eplivanserin induced a

significant increase of SWS duration coupled with a decrease in Stage 2, an increase in sleep efficiency and a decrease in the number of episodes of wakefulness after sleep onset. In parallel, the effects on SWS did not interfere with the physiological organization of sleep.

Eplivanserin is currently under development in chronic insomnia characterized by difficulties with sleep maintenance as measured by duration and number of nocturnal awakenings. Several in vitro studies in human biomaterials (and one study in non-human biomaterial) were conducted for predicting absorption, plasma protein binding and metabolic reactions (hepatic drug-drug interactions). The pharmacokinetic and pharmacodynamic properties as well as the safety and tolerability of eplivanserin were investigated in clinical studies including healthy subjects and patients.

II.2   The development programme/Compliance with CHMP Guidance/Scientific Advice

The development programme was initiated about 15 years ago. Eplivanserin was previously developed in several indications including:

- Obstructive Sleep Apnea Hypopnea Syndrome (OSAHS), where a formal CHMP scientific advice was given to the company in 2001 (CPMP/99/01 dated 26.01.2001)
- Fibromyalgia associated insomnia,
- Parkinson's disease ,
- Schizophrenia,
- Major depressive disorder (MDD),
- Alzheimer's disease (AD),

In the absence of conclusive results, the development was discontinued in these indications.

The clinical development program supporting the demonstration of the efficacy and safety of eplivanserin 5 mg/day in the treatment of insomnia with sleep maintenance difficulties consists of 4 randomized, double-blind (DB), placebo-controlled, efficacy and safety studies in adult and elderly patients with primary insomnia and sleep maintenance difficulties. A total of 2964 patients (1076 in the placebo group and 1888 in the eplivanserin 5 mg group) with primary insomnia were randomized in 4 Phase 2-3 studies.

Of note, a comparative double-blind, randomized study of eplivanserin 5 mg/day versus lormetazepam in the treatment of sleep maintenance insomnia for 4 weeks of treatment (Study EFC10480) is currently ongoing.

As regards to CHMP recommendations on the clinical development of medicinal products for the treatment of insomnia, the guidance "clinical investigation of hypnotic medicinal products" (dated 1991) still applies. However, it is currently under revision as hypnotics no longer cover the type of products currently developed in insomnia (with new mechanism of action). The new guideline "CHMP recommendations on the clinical development of medicinal products for the treatment of insomnia" was released for consultation in October 2009.

Finally, as above mentioned, a CHMP scientific advice was issued on 26/01/2001 under the reference CPMP/99/01 in the context of a previous development of eplivanserin in the treatment for obstructive sleep apnoea syndrome (OSAHS). However, no scientific advice for the development of the compound in the present intended indication has been requested by the company to the CHMP.

II.3   General comments on compliance with GMP, GLP, GCP

All eplivanserin studies are reported as compliant to GMP, GLP and GCP and followed the internationally agreed ethical principles.

II.4   Type of application and other comments on the submitted dossier

In general the dossier is well organized and it is easy to follow. However the overviews lack the required critical perspective on the shortcomings of the data.

III.   SCIENTIFIC OVERVIEW AND DISCUSSION

III.1   Quality aspects

Drug substance

Eplivanserin hemifumarate is a new chemical identity proposed for the treatment of insomnia. The molecule is described as slightly soluble in water and different conditions favouring the appearance of polymorphism show the molecule exists in only one polymorph. The structural elucidation comprises different methods which elucidate the stereochemical configuration around the two double bonds and support well the 2:1 ratio of the eplivanserin molecule relatively to the fumarate moiety. The study also includes X-ray single crystal analysis.

The approach of the impurity study including potential genotoxic is acceptable having also in mind information on the close part. Clarification was however requested on the absence of chromatographic evidence of this studies and lack of structural evidence for the impurities listed in tables included in this section. This evidence is given for the specified impurity and a synthetic impurity of the restrict part. The applicant provided in the course of evaluation structural evidence for the structural assignment as well as chromatograms for other impurities.   Specifications used to control the drug substance are satisfactory, and absence of some tests such as microbiological property and heavy metals have been justified by an historic of several batches already prepared. It is also justified the absence of control of some residual solvents, isobutanol and toluene, which validation should have been reported in the EDMF or applicant's part.

The stability data is satisfactory and demonstrates the relative stability of the substance to all ICH storage conditions. Stress studies show that only intense light is able to damage the substance in the solid state, but in solution this degradation is accelerated. Clarifications are asked on claimed structural assignment of some of the impurity products found. The mechanistic degradation pathway of some of two of this degradation product was not discussed. These impurities are detected as unspecified impurities. The certificates of analysis are also requested for at least three batches produced. Overall the EDMF open part is considered providing sufficient information and accurate information as well as the close part and data support the 24 month retest date claimed if protected from light.

Drug Product

The drug product (Sliwens) is in the form of pink film-coated footprint shaped tablets, containing 5 mg eplivanserin hemifumarate (base equivalent) for oral administration. Tablets are packed for commercial distribution in 100 count high-density polyethylene (HDPE) bottles and opaque PVC/aluminum blister packages with an aluminum foil lidding.

The physicochemical properties of the drug substance that are relevant for product performance were identified and assessed. The dosage form selected is a conventional film-coated tablet for immediate release after administration by the oral route. The selection of the excipients for the commercial formulation was based on the results from drug/excipient compatibility studies and on complete formulation development studies. Excipients are compendial and described in the Ph.Eur. Description of formulation development is satisfactory.

Process development and scale-up studies were carefully carried out and are described in a comprehensive manner. The commercial batch size is 350 kg, corresponding to 2,692,300 film-coated tablets and the manufacturing process is clearly described. It is a conventional tablet manufacturing process involving dry blending of the constituents. In addition, manufacturing process development has demonstrated the robustness of the process and showed that within the parameter ranges evaluated. The points/questions raised in the present assessment were in general suitably answered or clarified. However, a few important issues concerning drug product stability remain to be solved before marketing authorisation may be granted (please refer to the list of questions and answers below):

)   This justification for not reducing the shelf-life specification for SR46615A levels is not acceptable;

)   Although the new stability data is acceptable and support a shelf-life of 36 months, they also reinforce the objections raised concerning the levels of SR46615 remain since the far lower than the 1.2% specification. This issue may be accepted as a follow-up measure.

)   The justification for not conducting an in-use stability is not acceptable. These studies must be presented.

Based on the review of the data on quality, this application could be approved pending on satisfactory answer provided to other concerns in the List of outstanding questions.

III.2   Non clinical aspects

III.2.1 Pharmacology

Binding assays and modulation of receptor-mediated activity has been performed *in vitro*, *ex vivo* and *in vivo* in the mouse and in the rat.
Eplivanserin is a potent 5-HT2A receptor antagonist with a high affinity for human 5-HT2A receptors (IC50 = 0.89 nM), a somewhat lower affinity for human 5-HT2C receptors (IC50 = 10 nM), but no affinity for the 5-HT2B receptor (IC50>1 µM).
Eplivanserin also binds to 5-HT uptake site (IC$_{50}$ 610 nM), to human sigma-1 receptor (IC$_{50}$ 55 nM) and to human muscarinic M1 receptor (IC50 428 nM). In vivo experiments performed in the rodent confirmed the activity of eplivanserin based on antagonism of mescaline, L-5-hydroxytryptophan, tryptamine. Studies in mice confirmed the antagonist activity on sigma-1 receptor. Moreover, after subacute administration eplivanserin was found to up-regulate brain 5-HT2 receptors in rodents.
Eplivanserin has a low affinity for the rat calcium channel (IC50 = 590 nM for the diltiazem site, and 430 nM for the verapamil site), the human muscarinic receptor (IC50 = 428 nM in binding studies, representing weak antagonist activity [IC50 = 1.6-1.8 µM] in functional studies) and the human 5-HT transporter site (IC50 = 610 nM). No affinity for a wide range of other neurochemical sites, including the benzodiazepine sites associated with the effects of sedative-hypnotic agents were observed.
Since the highest individual Cmax value observed in humans after repeated administration of 5 mg/day eplivanserin does not exceed 60 nM, the compound is unlikely to interact substantially with any sites other than the 5-HT2A or 5-HT2C receptors, and to a lesser extent the sigma-1 receptor, when administered to patients.
Rationale to the claimed therapeutic indication was based on effects of eplivanserin on the sleep waking cycle and sleep wakefulness cycle in the rat using electroencephalographic activity.
Many experimental studies have shown a role for 5-HT and, in particular, an implication of the 5-HT2 receptor in the regulation of the sleep-waking cycle. The effects of eplivanserin on the sleep wake cycle and on EEG spectral parameters in rats are consistent with these data. The compound was shown to reduce REM sleep episodes, and to increase the energetic content of slow waves when administered in the light period. After acute administration to rats during the dark period, eplivanserin increased the mean duration of NREM sleep episodes, accompanied by a reduction of the mean number of slow-wave sleep episodes. In addition, during once-daily administration for 7 days, eplivanserin also reduced waking time and increased total NREM sleep time. A slight rebound of lower NREM sleep time was observed in rats 24 hours after the last dose, but sleep parameters had returned to normal values by 48 hours. The effects of eplivanserin on the sleep-wake cycle and on EEG spectral parameters in rats indicate that it acts to promote sleep maintenance. However, eplivanserin did not appear to induce sleep, nor showed sedative or myorelaxant properties similar to those observed with classical hypnotic compounds acting via the enhancement of GABAergic synaptic activity.

The two main circulating phase I metabolites of eplivanserin in humans are the N-demethyl (SR141342) and N-oxide (SR122504) metabolites. SR141342A is approximately five times less active in vivo on CNS 5-HT2 receptors than its parent compound, suggesting a lower capacity to enter the brain. SR141342A had a moderate affinity for some other neurochemical sites, including the human 5-HT uptake site (IC50 = 229 nM), the human sigma-1 receptor (IC50 = 290 nM), the human 5-HT2B receptor (IC50 = 460 nM), the human 5-HT7 receptor (IC50 = 620 nM), the human norepinephrine uptake site (IC50 = 520 nM) and the rat calcium channel (verapamil site, IC50 = 240 nM). SR141342A, like eplivanserin, was a pure antagonist at the sigma-1 site, possessing no agonist or partial agonist activity. The highest Cmax value of SR141342A after repeated daily administration of 5 mg eplivanserin does not exceed 35 nM suggesting that its binding to any site other than the 5-HT2A receptor after administration of therapeutic doses of eplivanserin is unlikely. SR122504 is about 35-

fold less potent than eplivanserin in terms of 5-HT2A receptor binding and has no affinity for the 5-HT2C receptor or for any other binding site investigated (IC50≥10 μM). Together with in vivo results, data suggest that whereas SR141342 may contribute to the 5-HT2A (and possibly sigma-1) antagonist activity of eplivanserin in vivo, the other metabolites are unlikely to participate in the pharmacological effects observed after eplivanserin administration.

Secondary pharmacodynamics indicated that eplivanserin possesses antidepressant-like activity in a number of classical laboratory models but had no anxiolytic activity. It inhibited platelet aggregation and thrombus formation in vivo in different animal models and exhibited hemorrhagic properties *in vivo*.

Safety Pharmacology: Cardiovascular safety pharmacology studies showed that eplivanserin and SR141342 blocks human ether a-go-go-related gene (hERG) potassium channel blockade *in vitro* with ratio of exposure of 62 and 534 for eplivanserin and SR141342, respectively, based on plasma concentration in humans at the intended therapeutic daily dose of 5 mg. Because the hERG data suggest eplivanserin had the potential to prolong the QT interval, additional *in vitro* studies were conducted in Purkinje fibers eplivanserin without effects at 1 μM (328 ng/mL), representing 26-fold the Cmax in humans. The Applicant has compared this ratio to the historical prototype 5-HT2A receptor antagonists ritanserin and ketanserin occasionally studied for comparative purposes in primary pharmacology studies. Eplivanserin displays a binding on the rat L-type Ca2+ current (the IC_{50} being 430 nM), functionally associated with a significant percentage of inhibition (92%) at 10 μM, ie, at concentrations similar to those producing inhibitory effects on the repolarizing hERG potassium channel. On the isolated canine Purkinje fibers, this effect on Ca2+ channel may account for the decrease in APD50 and APD70 noted in the dog Purkinje fibers (-21% and -17%, respectively, at 10 μM). As APD90 is not modified in this model at the same concentration, it is most likely that the concomitant inhibition of hERG and Ca2+ channels lead to a compensation of the respective effects on APD.

In summary, the Applicant compared the ratio of concentrations derived from hERG IC_{50}, canine Purkinje fibers studies and human plasmatic exposure to the historical prototype 5-HT_{2A} receptor antagonists ritanserin and ketanserin, leading in conclusion that the ratios of concentrations of ketanserin and ritanserin inducing effects in *in vitro* models to the human maximal plasma concentration at therapeutic dosages appeared lower than that observed with eplivanserin.

In dogs, following intraduodenal administration, no change in ECG parameters was observed. Based on these elements, the MAH has complied with ICH E14 note for guidance and provided a study of a single dose of eplivanserin effect on QT interval in healthy volunteers, at a maximal dose that represents 2 fold (10 mg) the therapeutic dosage (5 mg).

In the telemetered baboon, eplivanserin induced a slight hypertensive effect (10 to 20 mmHg) from 8.5 mg/kg upwards; at this dose, exposure to eplivanserin was estimated to be 924 ng.h/mL, based on exposure values at 10 mg/kg in the male baboon as determined in another study, representing 4.2-fold exposure in humans at the intended therapeutic dose (5 mg/day). At the repeated dose of 85 mg/kg/day, eplivanserin induced the same hypertensive effect with inhibition of reflex tachycardia, and a bradycardia (-39% versus baseline). Serotonin is documented to induce an increase in heart rate in several species, via the activation of myocardial receptors (in the rat), or a 5-HT2 receptor-mediated release of catecholamines from the adrenomedulary cells (in the anesthetized dog), or by central mechanisms involving 5-HT2 receptors. It is therefore possible that the bradycardia observed in the conscious animal as well as the slightly decreased blood pressure noted in anesthetized dog are secondary to the antagonist activity on 5-HT2A receptors. By contrast, no clear mechanism could be identified that could account for the increase in blood pressure noted in the telemetered primate. All changes noted in the conscious animal were rapidly and totally reversible.

Eplivanserin produced effects on CNS in mice limited to a slight reduction in body temperature (≥25.5 mg/kg), a significant reduction in locomotor activity (≥2.55 mg/kg), and a small degree of motor incoordination (≥25.5 mg/kg). No effect was observed on gross behavior (up to 85 mg/kg) and muscle relaxant activity (up to 85 mg/kg). Eplivanserin showed no anticonvulsant properties (in the model of seizures produced by electroshock [up to 8.5 mg/kg]) or proconvulsant properties (in the model of seizures induced by pentetrazol, up to 100 mg/kg), and did not show anticholinergic activity (up to 25.5 mg/kg) or potentiation of the sedative effect of ethanol in mice (up to 85 mg/kg).

Eplivanserin has no affinity for most sites that have been linked to drug abuse potential but displayed a moderate affinity for the sigma-1 receptor (IC50 = 55 nM), which stimulation has been associated with potential drug abuse, as their activation is observed after administration of drugs such as cocaine or ethanol and stimulation of 5-HT2A receptors has also been associated with the effects of hallucinogenic drugs of several chemical classes. Eplivanserin was found to possess no agonist or partial agonist activity at either the 5-HT2A or the sigma receptor, but to fully antagonize the effects of agonists at these sites, both in vitro and in vivo which might suggest that eplivanserin is not susceptible to elicit drug abuse. Eplivanserin has previously been found in laboratory paradigms to antagonize a number of behavioral effects of drugs with abuse potential.

In vivo respiratory studies (pentobarbital-anesthetized dogs, intraduodenal route, 30 and 60 mg/kg) showed a slight increase in respiratory frequency (maximum +10 cycles/minutes) and flow (maximum +60%), without change in tidal volume ($\geq$30 mg/kg). In the conscious rat, no respiratory depressant effects were observed.

Mild effects were noted on renal function and consisted of a natriuretic effect, observed in male and female rats at doses from 30 mg/kg, respectively, and a decrease in endogenous creatinine clearance (-14% to -40%) in females at doses $\geq$30 mg/kg. Effects on gastrointestinal system were limited to an inhibition of gastric emptying in rats at 30 mg/kg, and a slight reduction of gastric pH in rats at 10 mg/kg, but no gastric ulcerogenic effects were observed up to 30 mg/kg in rats. In mice receiving 30 mg/kg, no modification of the intestinal transit was observed.

Eplivanserin showed a weak potential to induce increases in plasma prolactin levels in female rats after a single dose of 90 mg/kg. Although effects were slight after single administration, they are consistent with the hyperprolactinemia observed in female rats in the 6-month toxicity study.

III.2.2 Pharmacokinetics

Pharmacokinetic studies were performed on mouse, rat, baboon and rabbit. A high performance liquid chromatography-ultraviolet (HPLC-UV) method was first used and then a liquid chromatography tandem mass spectrometry (LC-MS/MS) was developed. These methods fulfilled the criteria for validations. The early methods are specific against the E/E-isomeric form of eplivanserin, SR46615. The later methods allowed the resolution between compounds of interest, eplivanserin and SR141342 (N-demethyl metabolite) and their E/E isomeric forms, SR46615 and SR141343, respectively.
Studies were conducted mainly via the PO route of administration as the intended therapeutic route. During studies conducted by a PO route, eplivanserin was administered using a 10% aqueous gum Arabic solution, or a 0.6% methylcellulose aqueous solution, as for toxicology studies (exposure achieved with both vehicles being overall consistent). For studies conducted by the IV route, a 10% aqueous PEG 400 solution was used.

III.2.2.1 ABSORPTION AND BIOAVAILABILITY

The absorption of eplivanserin was close to 100% in rats and in baboons but bioavailability of eplivanserin was variable with 82% in female rats, 33% in male rats and 9% in male baboons. Bioavailability was higher in female than in male rats. For SR141342, no major difference in exposure was observed between female and male rats.
In the two-year studies, whatever the sex and whatever the dose group, SR141342 represented from 32% to 49% of the eplivanserin exposure in mice and from 25% to 33% in rats. After a 14-day repeated administration, SR141342 exposure represented 70% of that of eplivanserin in baboons.
In mice, from 125 mg/kg/day and above, a 2- to 3-fold decrease in eplivanserin exposures was observed from Day 1 to Day 29, consistent with the auto-induction process observed in mice from these doses. A 4- to 5-fold increase in eplivanserin and SR141342 exposure was observed following repeated oral administration in rats, while no significant accumulation of parent drug and SR141342 was observed in baboons. Eplivanserin exposures were generally higher in male than in female mice (up to 3-fold), and 2- to 4-fold higher in female than in male rats (consistent with higher oral bioavailability observed in female rats). No major gender effect was observed in baboons. No major gender effect was observed in rodents and baboons for SR141342 exposures.

III.2.2.2 DISTRIBUTION AND PROTEIN BINDING

Eplivanserin is widely distributed within the body. Vd were 9 L/kg and 6 L/kg in rats and baboons, respectively. Eplivanserin was rapidly and widely distributed in most of tissues and organs including brain and bone marrow, up to 1 to 2 hours after dosing, with highest levels in the liver and the kidney. Overall, similar tissue distribution pattern was observed for both genders, and following both either single or repeated administration. No significant binding of eplivanserin to blood cells was observed. Plasma protein binding of eplivanserin was similar among species, from 77.7% to 83.1% in mouse, rat, rabbit and baboon. For SR141342, fractions bound were found to be similar among species, from 77.8% to 87.0% in mouse, rat, rabbit, dog, baboon and human. Studies conducted on human plasma samples showed similar findings with a mean fraction of eplivanserin and SR141342 bound to plasma proteins of 81.5% - 82%.

Eplivanserin and its metabolites cross the placental barrier. A penetration of radioactivity into embryo (Day 9) or fetus (Day 18) was observed after administration of [14C]-eplivanserin to pregnant Sprague-Dawley rats, with a fetus to maternal plasma ratio of about 1.36 and 2.25, 2 and 24 hours post dosing, respectively, at Day 18 of gestation. The placental transfer was also assessed in pregnant New Zealand rabbits at Day 12 and Day 18 of gestation. On Day 12, total radioactivity was detected in amnios, placenta and trophoblast, without retention at 24 hours. On Day 18, eplivanserin and SR141342, were observed in the foetus homogenate, as free forms and glucuronic acid conjugate forms showing the ability of eplivanserin and its metabolites to cross the placental barrier.

III.2.2.3 METABOLISM

In liver microsomal fractions, in all species tested, two main pathways of oxidation were characterized, leading to *N*-demethyl derivative, SR141342, and hydroxyl derivatives (at different sites), and one pathway of glucuronidation. Eplivanserin oxidation was higher in rodents, rabbits and dogs (from 75.4% to 95.9%) than in non-human primates and humans (22.2% to 44.4%). The rate of glucuronidation was highest in guinea pigs and rabbits (>95%) and lowest in baboons and humans (<5%). The same metabolites were detected in the various species, although some quantitative differences were noted. In addition, this study allowed to demonstrate that the cytochrome P450 3A isoenzyme was mainly involved in the N-demethylation process.

Following incubation of [14C]-eplivanserin in liver subcellular S9 fractions from Aroclor induced Sprague-Dawley rat, the two main oxidative pathways were observed, N-demethylation leading to SR141342 and N-oxidation leading to SR122504. Other minor metabolites were detected and identified mainly as hydroxy derivatives. These findings showed that the oxidative metabolism of eplivanserin observed in these particular conditions was consistent with that previously observed on liver microsomal fractions, ensuring that all relevant oxidative metabolites were formed during the in vitro genotoxicity tests using S9 fractions.

In vivo in mice, rats, rabbits and baboons, eplivanserin undergoes extensive metabolism to numerous metabolites after oral administration, and the unchanged compound was often detected as a minor compound regardless of the biological fluids, except in baboon urine and feces.

The main routes of biotransformation regardless of the species consisted in:
- *N*-oxidation leading to SR122504 with further glucurono- and sulfo-conjugation,
- *N*-demethylation leading to SR141342 with further glucurono- and sulfo-conjugation,
- Glucurono- and sulfo-conjugation (SR90190) of the parent compound.

The main circulating metabolites were glucuronide derivatives of either the parent compound or the *N*-demethyl metabolite (SR141342) in all nonclinical species. The overall qualitative metabolism pattern is similar across species including human. All metabolites identified in human were also identified in at least one nonclinical species, except 5 metabolites observed in human urines and representing a very minor percentage of the dose excreted (up to 2.0%). These metabolites are not circulating in plasma, are all conjugate derivatives, and are all related to existing metabolic pathways in nonclinical species.

All metabolites representing more than 10% of eplivanserin systemic exposure in human are considered adequately characterized in nonclinical toxicity studies conducted with the parent compound, and no specific toxicity study was conducted.

In vivo, eplivanserin is an inducer of cytochrome P450 (CYP)1A, CYP2B, CYP2C and CYP2E in rodents, from 25 mg/kg/day in mice and from 60 mg/kg/day in rats. This effect was more pronounced on CYP2B enzyme activity (increased by 10- to 50-fold) than on other cytochromes (increased by 2- to 4-fold). Only a slight (1.3- to 1.6-fold) induction of CYP2C was observed in baboons (from 30 mg/kg/day). In addition, eplivanserin is an inducer of CYP3A in mice (2.5- to 4-fold), while the CYP3A was not modified in rats or baboons.

Accordingly, an auto-induction process was only observed in mice, resulting in a 1.5- to 2-fold increase in eplivanserin metabolism (from 125 to 400 mg/kg/day). This auto-induction process is consistent with the 2- to 3-fold decrease in eplivanserin exposures observed between Day 1 and Day 29 during toxicokinetic study, from 125 mg/kg/day and above in mice.

Overall, the significant induction effect seems to be limited to rodent species, and was observed to a lesser extent in baboon (only for CYP2C). Induction of CYP3A4, the only CYP involved in the metabolism of eplivanserin, was only observed in mice. Enzyme induction was not reported in human.

III.2.2.4 EXCRETION AND ELIMINATION

In rats and baboons, the pharmacokinetics of eplivanserin, after a single IV administration, was characterized by a high plasma clearance (close to 7 L/kg/h in rats and 2 L/kg/h in baboons) and a short terminal half-life (0.9 hour in rats and 2 hours in baboons).

Eplivanserin excretion is rapid, particularly in mice and rats, with more than 80% of the administered radioactivity dose recovered during the first 24-48 hours post dosing, and almost complete with more than 90% to 95% of the administered dose excreted over 168 hours in rats and 264 hours in baboons, following both PO and IV routes. Radioactivity was mainly excreted in urine in male mice (60%) and in feces in female mice (53%). In rats, fecal excretion prevails (around 60%) and is larger than that in baboons, for which the excretion is balanced between urine and feces. Unchanged eplivanserin accounted for less than 15% of the dose excreted in urine in mice, rats and baboons, suggesting that eplivanserin was eliminated mainly by metabolism. The daily excretion of radioactivity in urine and feces remained in the same order of magnitude from Day 1 to Day 14. Milk excretion of radioactivity was demonstrated in rats (0.13% of [14C]-eplivanserin derived radioactivity was excreted in the milk within 24 hours).

III.2.3 Toxicology

The toxicological profile of eplivanserin and the main human metabolite was fully characterized in a set of single and repeated dose studies in rodents and nonrodents (baboons), the latter selected on the basis of the kinetic similarities to humans, genotoxocity, carcinogenicity, reproductive toxicity, and additional studies addressing other aspects like phototoxicity, immunotoxicity, sensitization potential or local tolerance.

General toxicity

By the oral route, the maximum nonlethal dose was 750 mg/kg in male and female mice, 1000 mg/kg in male rats and 500 mg/kg in female rats. Central nervous system disorders associated with signs of health deterioration (convulsions, prostration and decubitus, piloerection), and decreased body weight gain were observed in both species from 500 mg/kg upwards PO. No mortality was observed in baboons but a hypertensive effect from 8.5 mg/kg upwards and a reduction in baseline heart rate.

After repeated administration, decreased food consumption and decreased body weight gain were recorded in all species. In all species effects were dose-dependent, at exposures which in some cases were close to the expected in the clinical setting. Whether this effect is pharmacologically driven is not clear. The applicant has presented a number of reasons to base their belief that there is no support for a dopamine-mediated effect on the observed decrease in food consumption and increased body weight. Also the involvement of 5–HT receptor modulation has been commented. The conclusion is that dopamine agonistic and antagonistic effects would have to be present for the effects to be justified, despite the agreement that a cross talk between dopamine and serotonin receptors exists. Concerning the considerations on the possibility for dopamine effects to be related to the animal findings under discussion, the Applicant did not consider the possibility for both agonistic and antagonistic dopamine receptor activity to be present at different receptor subtypes. Indeed, for instance it is recognized that D5 receptors are involved in the craving and modulate food

consumption, while other systems are involved in prolactin modulation or in hormone effects. In baboons, a dependency of effects on body weight and food intake to gastrointestinal effects, ie emesis, could be established at high doses in several animals. In the baboon, these effects were usually transient, lasting from 1 to several weeks, and then followed by normalization while animals were still under treatment.

CNS effects: the main target organ of eplivanserin is the central nervous system (CNS) in both single-dose (mice and rats) and repeat-dose toxicity studies (mice and baboons). Mortality associated to neurological disorders (mainly convulsions) occurred at high doses (250 mg/kg/day in mice and 60 mg/kg/day in baboons). In baboons the threshold for induction of neurological disorders could be 30 mg/kg/day. The baboon appeared to be the most sensitive species for CNS effects. In this species, the ratios of exposure vs humans to eplivanserin and SR141342 at the NOEL for CNS effects were 12 and 9 respectively. Eplivanserin did not present proconvulsant properties at doses up to 100 mg/kg (IP) but convulsive events were noted in animal studies.

Cardiovascular function: cardiovascular effects consisted of bradycardia, both in rats and baboons, considered as the expression of pharmacological properties of eplivanserin; it appeared from 30 mg/kg/day upwards in rats and 12 mg/kg/day in baboons. Although the QT was increased in some cases as a reflection of bradycardia, no changes in QTc occurred in any instances. Amplitude was slightly dose-related, as well as related to exposure, but did not appear to progress with time. Additional changes recorded in baboons consisted of (slight) increases in mean arterial pressure. The observed modifications (bradycardia in rats and baboons and increased blood pressure in baboons) remained relatively low in amplitude, did not show progression with time, were well tolerated over long-term administration, were not accompanied by any histopathological cardiovascular modification, and were totally and rapidly reversible. At least in the two animals, which, after the repeated administration phase (19 days), were surveyed for two additional weeks after the treatment was stopped, the reversibility was also seen. However a mechanistic explanation has not been obtained. In their response to a question posed by CHMP the Applicant has provided further arguments and the clinical relevance remains to be clarified and discussed. Although evidence for inhibition of platelet aggregation and hemorrhagic effects related to the pharmacological activity (5-HT2A receptor antagonism) of the compound was noted in pharmacology animal models, no changes were observed in repeat-administration studies suggestive of prohemorrhagic activity of eplivanserin in vivo. A further revision of animal events has been provided by the Applicant. In addition, the evidence that clinically no concern has been raised is also referred.

Despite the apparent lack of interaction of eplivanserin with 5-HT_{2B} receptors, it still has some affinity for the human 5-HT transporter. However**,** the data obtained in preclinical studies with eplivanserin actually does not speak in favor of a mechanism reported by Elangbam *et al*. Moreover, valvulopathy has not been observed as well with many other, much more potent inhibitors of the human 5-HT transporter than eplivanserin. Indeed, according to the hypothesis of Elangbam, practically all the tricyclics and the selective serotonin reuptake inhibitors (SSRIs) could be suspected of leading to enhanced 5-HT_{2B} receptor stimulation, to a much greater degree than eplivanserin, since their clinically active blood levels (unlike those of eplivanserin) should clearly reduce 5-HT transporter function in vivo as this is their mechanism of action. However, this has not been observed among the millions of patients treated with these agents over the last 50 years.

Gastrointestinal function: gastrointestinal changes (in particular emesis in baboons) appeared from 20 mg/kg/day upwards. Effects on body weight gain and food intake appeared from 10 mg/kg/day upwards in rats (6 month study), and from 12 mg/kg/day upwards in baboons (1-year study). In the baboon, emesis was partly responsible for the effects noted on food consumption and body weight, and was possibly related to impairment of gastric emptying (as noted in the cardiovasular telemetered study as well as in rats (safety pharmacology), but as referred a pharmacological basis for weight decrease was not discarded.

Effects on hematological and blood biochemical parameters, and histopathological changes: slight decreases in cholesterol (maximal of ~ -30%) were noted in baboons from 5 mg/kg/day upwards, but the variations remained close to lower historical values in controls. An increase in cholesterol was noted in rats from 20 mg/kg/day upwards, males being more susceptible than females. Overall, the cholesterol changes observed with eplivanserin in preclinical species were not considered of relevance for risk extrapolation to humans, since they are related to enzyme

induction (in rodents), a phenomenon not occurring in humans with eplivanserin, or are beneficial rather than deleterious from a clinical standpoint (as regards decreases in LDL lipoprotein fraction as observed in baboons).

Moreover, there were no clinically significant changes in total cholesterol and triglycerides parameters in patients treated with eplivanserin at the therapeutic dosage (5 mg/day) during the clinical trials.

The increases in vacuolation in lung, corpora lutea and adrenals noted at high doses in the rat 4-week study were proposed to be at least partly related to the increased plasma cholesterol levels. These observations appeared to be limited to this species and were not observed in other species, including primates. Increases in transaminases (ALT and AST) and/or ALP were noted in both rodents and baboons, at high doses (from 125 mg/kg/day upwards in mice, from 100 mg/kg/day upwards in rats, and from 60 mg/kg/day upwards in baboons). Elevations remained slight, limited to 1.5- to 2.5-fold increases when compared to control values. No morphological changes suggesting hepatocellular degeneration or necrosis were observed in rats or baboons. The (slight) increased incidence of focal hepatocellular necrosis observed in males only at 30 mg/kg/day in the carcinogenicity study was not noted previously at the same dose given for 6 months, or in females at higher dosage and exposure. Also, no changes occurred which may suggest cholestasis, in any species. Evidence of hepatic steatosis was found in the mouse, the rat and the baboon. In the mouse, increased incidence in hepatic steatosis, was found from 25 mg/kg/day upwards, as well as increases in single-cell necrosis but hepatocellular steatosis was not found in the mouse carcinogenicity study. In the rat centrilobular/mediolobular microvacuolar steatosis occurred only at the high dose (180 mg/kg/day) in the 4-week study. In the baboon, hepatic macrovacuolar steatosis occurred also at high doses (≥60 mg/kg/day), and could be in some cases related to the health deterioration of the animals at the dose of 100 mg/kg/day. In primates, no biological or morphological sign of hepatocellular injury was observed up to the dose of 30 mg/kg/day, where exposure in parent compound (2960 and 2130 ng.h/mL in males and females, respectively) is approximately 10- to 15-fold the human exposure after a 5 mg repeated administration. In the mouse, liver enzyme induction occurred from 25 mg/kg/day upwards and was more pronounced in males than in females, while in rats it occurred from 30 mg/kg/day upwards and was more pronounced in females than in males, in relation with higher exposures to eplivanserin and metabolite SR141342 achieved in female rats when compared to male rats. In the rat, the induction was of the "phenobarbital-type", i.e. with prominent increase in CYP2B activity. On the contrary, induction in the baboon (from 30 mg/kg/day upwards) remained modest, and limited to slight increases in the CYP2C activity. Because of this difference, changes related to induction in rodents were claimed as not relevant to primates, including tumoral changes. In addition, no induction was referred to be noted in humans in vitro and in vivo studies.

A tabular summary of the liver effects in the different studies and species has been provided showing that liver enzyme induction could be related to the effects in rodents. In baboons, a plausible explanation was provided for steatosis, which included cellular "stress" at high exposures. In addition sufficiently high safety margins were identified, and no signals of concern were identified in clinical trials. It is considered that the concern has been sufficiently addressed, evaluated and clarified. No further discussion is considered needed.

In baboons after repeated administration blood in urine was observed in the 6 months study without histopathological correlation. In rodent carcinogenicity study, hyperplasia was observed in urinary bladder. No plausible explanation is anticipated.

The data subsequently presented by the Applicant pointed towards an effect which remains not well explained in rodents, but that was less apparent in baboons, where the incidence of blood in the urine of controls and treated animals at the different treatment periods was not substantially different. No effect was reported in patients. Nevertheless, since the number of non-human primates and subjects observed in the clinical trials might have been limited, the need to further follow this event clinically, e.g. monitoring haematuria in patients, should be addressed or better explained.

The Applicant is asked to comment on a possible relationship of these findings and on the potential for eplivanserin to induce bladder toxicity, as well as the possible mechanism.

Hormonal function: a decrease in prolactin was originally reported in the male rat (≥3 mg/kg/day) and was considered rather as an artefactual change due to the relatively high values noted in control

males in the 6 month study. The increase in prolactin noted in females in this study correlated to a slight extent with the observation of a slight increase in prolactin in a study performed after a single administration of eplivanserin at 90 mg/kg. The increase in prolactin did not result in proliferative changes in mammary gland in rodents and was not observed in the baboon. Its relevance to humans is not known. Whether it is related to the reduction of the mammary gland function observed in rodents has not been discussed. Furthermore, a mechanistic explanation for this finding was also not given. The Applicant proposes that the prolactin effects of eplivanserin might be clinically irrelevant because they could be rodent specific. This is acknowledged. However, the accuracy of the clinical evaluation of this aspect needs to be characterized before clinical irrelevance is declared.

Safety ratios in general toxicity studies
The NOEL was 2.5 mg/kg/day in mice in the 3-month study. In rats in the 6-month study, the NOAEL was 3 mg/kg/day, and effects noted at 10 mg/kg/day were considered as minor since limited to a decrease in body weight gain and food intake. In the baboon, the NOAEL was 5 mg/kg/day in the 1-year study. Effects at 12 mg/kg/day in the 1-year study were considered as minor since limited to mild, reversible bradycardia. Exposures achieved in rodents and baboons at these doses (in the 13-week study in the mouse, the 6-month study in the rat and the 1-year study in the baboon) for eplivanserin, provide safety ratios as presented in Table 1 below, when compared to exposures in humans for a daily dose of 5 mg. Ratios at the NOAEL in rats, i.e. 3 mg/kg/day, are provided based on exposure obtained in the carcinogenicity study at the same dose level. Although SR141342 was not administered alone to characterize its specific toxicity profile, its contribution to the overall toxicity of eplivanserin was thoroughly evaluated, since exposure to active metabolite (SR141342) was documented in both species (in at least one repeated administration study), and was shown to represent 25% to 33% of the parent compound exposure in rats and 70% in baboons whatever the sex and the dose, providing evidence for the assessment of its toxicological properties in all in vivo studies. Overall, safety margins are well documented for both eplivanserin and SR141342, and ensure the safe use of eplivanserin at the therapeutic dose of 5 mg once daily in patients, with respect to the toxicological risks identified in the rat and the baboon.

Table 1. Exposure ratios at NOAELS vs clinical exposure in general toxicology studies

Species	Study N°	Dose (mg/kg/day)	C_{max}	AUC_{0-24}
		Based on eplivanserin exposure parameters		
Mouse	DDC0004	2.5	1.6-1[a]	0.3-0.1[a]
Rat	TXC0912	3 (NOAEL)[b]	0.03	0.003
		10[c]	2-7.6[a]	0.2-2.8[a]
Baboon	TXC1010	5 (NOAEL)	5.1	1.4
		12	17	5.5
		Based on SR141342 exposure parameters		
Mouse	DDC0004	2.5[d]	0.8	NA
Rat	TXC0912	3[e]	NC	NC
		10[c]	1.2 – 4.7[a]	0.8 – 0.6[a]
Baboon	TXC1010	5 (NOAEL)[f]	5.7	2.4
		12[f]	14	5.8

Additional information / abbreviations: Ratios are calculated based on exposures in human subjects as determined in the POP PK analysis, ie: eplivanserin: C_{max} = 12.5 ng/mL, and AUC_{0-24} = 220 ng.h/mL; SR141342: C_{max} = 5.34 ng/mL, and AUC_{0-24} = 122 ng.h/mL (see 2.7.2 – [Section 3.3.1]).
C_{max}: maximum plasma concentration observed; AUC_{0-24}: area under the curve plasma concentration versus time from 0 to 24 hours
NOAEL: no observed adverse effect level, NA: Not available, NC: Not calculable
a: male-female values
b: no data available in TXC0912, ratios calculated from exposures in the carcinogenicity study at Day 29 (2.6.7, Study CAR0025 [TS 2.6.7.10C]) males only, from concentrations quantified up to 2 hours only
c: no data available in TXC0912, ratios calculated from exposures in the carcinogenicity study at Day 29 (CAR0025)
d: no data available in DDC0004, ratios based on exposures extrapolated from values at 0.85 mg/kg single dose in Study ABS0499 (see 2.6.5 [TS 2.6.5.3])
e: no data available in TXC0912;
f: no SR141342 data available in TXC1010, ratios based on exposures extrapolated from values at 10 mg/kg/day in Study RDS0011 (see 2.6.5 [TS 2.6.5.4]) on Day 14

Genotoxicity

Eplivanserin was tested for its genotoxic potential in a comprehensive battery of in vitro and (several) in vivo tests. No genotoxic response was observed in the Ames tests, the in vitro DNA repair assays, and the V79/HGPRT (hypoxanthine guanine phosphoribosyl transferase) gene mutation assay. Positive responses were obtained in the in vitro mouse lymphoma assay both in the absence or presence of metabolic activation (from 5 μg/mL without S9 and from 20 μg/mL with S9, upwards), and in the first in vitro assay in human lymphocyte in the presence of metabolic activation (from 115 μg/mL upwards); this effect was not confirmed in the second in vitro assay in human lymphocyte at concentrations up to 200 μg/mL in presence of metabolic activation, in which effects were only observed at cytotoxic concentrations. The in vitro results were not confirmed in several in vivo tests performed including i) in vivo micronucleus tests in mice and rats ii) Comet assay (on liver cells and bone marrow cells from female rats) and iii) the mutation assay in the MutaTMMouse. Sufficiently high exposures were reached in the animals. However from the *in vivo* tests performed a marginal response was noted in the single-administration in vivo DNA repair test after 15 hours of exposure only, at doses of 500 and 750 mg/kg, without dose-related effect. However, no response was observed at the 2.5 hours timepoint and no effect was detected in the repeat-administration (7 days) in vivo DNA repair test, at doses up to 300 mg/kg/day (sampling 24 hours after the last exposure). Taken together, the negativity of the in vivo tests performed together with that of Ames test seem sufficient to discard the concern that might have been raised from the positivity of the chromosomal aberration tests in vitro. Eplivanserin does not appear to be genotoxic.

Carcinogenicity

Life span carcinogenicity studies were performed in mice and rats. In mice hepatocellular adenomas and carcinomas were observed with a low safety margin at the NOAEL. Other non neoplastic findings which may deserve clarification include urothelial hyperplasia and inflammation. A mechanistic explanation for the mice hepatocarcinogenesis has been investigated, through the classical liver enzyme approach, which was confirmed for doses close to the carcinogenic ones, in special for CYP2B. In rats liver adenomas were observed in females only, at a low incidence. A compilation of CYP increases observed in all animal species during preclinical trials has been subsequently provided. These data show that the main effect in rodents consist of increases in CYP2B activity, while other CYPs activities are increased to a much lower extent, and that male mice and female rats show the highest rate of increase in the CYP2B activity, corresponding to a phenobarbital-type induction.

Reproductive function

No effect on reproductive parameters was noted in male rats. Irregular estrous cycle (≥10 mg/kg/day), and slight increase in postimplantation losses and decrease in the number of corpora lutea (≥30 mg/kg/day) occurred in female rats. With regard to cycle irregularities, effects were not dose-dependent, and in repeat-dose toxicity studies, no effect was histologically observed in the distribution of the phases of the estrous (rats) or menstrual (baboons) cycle after 6 months (rats) or 1 year (baboon) of treatment. These effects were likely related to increases in prolactin levels in females, which are known to result in rodents in estrous cycle perturbations and decrease in ovulation. Since no blockade of the cycle was observed in either rat or baboon, and since no prolactin changes were observed in baboons or in humans in clinical trials, the relevance of rat changes in estrous cycle to women is not clear, but it is acknowledged that prolactin has different effects in rodents and humans.

The Applicant should comment on the evidence collected clinically with eplivanserin that could confirm the presumption that no effect on fertility of oestrus cycle is observed.

No teratogenic effect was observed in rats at doses up to 60 mg/kg/day in pregnant females in the definitive study. In the preliminary study, malformations were observed at maternally toxic doses (from 200 mg/kg/day, including lethality), and a limb malformation (bending of long limb bones) was noted in one fetus at 60 mg/kg/day. The significance of this latter observation regarding the threshold of dysmorphogenic effects remained doubtful since it was not observed in the definitive study conducted in a larger number of animals. It was considered that these effects could be secondary to prominent maternal toxicity, as the spectrum of changes observed at high doses (in particular shortening or bending of long limb bones, and cleft palate) was consistent with that described in literature to be noted in association with maternal toxicity in the rat. At 60 mg/kg/day, exposures to eplivanserin in female rats (in the carcinogenicity study were Cmax = 770 ng/mL and AUC = 9500 ng.h/mL, representing 62-fold and 43-fold the Cmax and AUC values in human at daily therapeutic

dose (5 mg), respectively. At the NOEL for developmental effects in the rat (20 mg/kg/day) exposures (AUC) in the nonpregnant female are estimated 2513 ng.h/mL for eplivanserin and 734 ng.h/mL for SR141342 (based on exposure data in carcinogenicity study), representing 11-fold and 6-fold respectively, the human exposure at the daily therapeutic dose (5 mg).

In the rabbit, embryolethality was observed at 400 mg/kg/day in the context of maternal toxicity in the first study. Isolated fetal anomalies occurred in this study. Few cases of spina bifida were observed across the two studies. The incidence of this observation, which is not a common one, did not display a dose-dependent incidence. Cases of spina bifida were spina bifida aperta or occulta in different studies. The Applicant has undergone an extensive discussion to defend that these findings were incidental and not related to eplivanserin treatment.

At 200 mg/kg/day, the fetus of 15.9 g also had other malformations (anal atresia and tail limited to a fusion of the first 4 caudal vertebrae, 1 kidney and ureter absent) and signs of marked growth retardation (testes not descended). It has been proposed by the Applicant that, in the affected rabbits, because of their occurrence in very small fetuses, it is possible that the abnormality of vertebral arches and omphalocele resulted from the effects of eplivanserin on maternal body weight, which led to perturbation of embryofetal development, rather than from a direct effect of eplivanserin on the developing conceptus.

Cranial defects involving the neural tube are rare but regularly noted in the NZW rabbit. One domed head, one meningoencephalocele, one cranioschisis and craniorachischisis were observed between 1997 and 2007 in NZW/INRA 1077 rabbits, with a maximal fetal incidence per historical control group of 0.6%, versus 1.2% in the high-dose group at 300 mg/kg/day. In addition, historical data from CIT described 1 acephalostomia and 1 meningocele with a maximal fetal incidence per control group of 0.7%. The historical incidences of these findings relative to those observed at 300 mg/kg are in general consistent to one another. Although collectively the neural tube defects could reflect the spontaneous background of this strain of rabbit supplied by LAGO, NZW/INRA 1077, an involvement of eplivanserin in the aetiology of this type of malformation cannot be excluded.

Besides these effects, evidence of embryofetal toxicity was indicated by decreases in fetal weights and litter size from 130 mg/kg/day and embryolethality at the highest dose (400 mg/kg/day). However, the slight increase in the number of resorptions at 300 mg/kg/day in the study TER0572 was not clearly attributed to treatment with eplivanserin, since values remained with the range of historical data. These embryotoxic effects were most likely the consequence of significant maternal toxicity at this dose, since body weight loss and food deprivation in pregnant rabbits are known to result in abortion, fetal mortality, and decreases in litter size and in fetal and placental weights.

Overall, in the rabbit, an increase in malformations occurred at high doses. A direct effect of eplivanserin could not be dismissed, but it is noted that the findings occurred in groups in which there was maternal toxicity, which may have played a significant role in the genesis of these anomalies. Overall, considering the two main studies, the maternal and developmental NOEL was considered to be 40 mg/kg/day. No exposure in pregnant rabbits was available at this dose. At the dose of 130 mg/kg/day, exposures (AUC) to eplivanserin and SR141342 were 1350 ng.h/mL and 1020 ng.h/mL, respectively, representing 6-fold and 8-fold the AUC of these compounds at the daily therapeutic exposure in man (5 mg). With regard to eplivanserin peri- and postnatal toxicity, a decrease in body weight and survival was noted in pups in the early postnatal period ($\geq$5 mg/kg/day). Eplivanserin induced no effect in developmental and sensorial/behavioral parameters in the newborn, except for a slight delay in the surface righting reflex, which was secondary to the decrease in body weights in the pups. In the preliminary segment I/III study, no milk was found in the stomach of the decedent pups and an inactive aspect of mammary gland was observed at macroscopic examination. This observation indicated a failure of dams to nurse the pups. The mechanism of this failure remained undetermined. It could be due to a primary decrease in mammary gland production (resulting into pup decreased weights and mortality); however this was not consistent with previous record of increased prolactin levels in the nonpregnant female rat. Also a defect of pups in suckling, resulting in a relative inactivity of the mammary gland due to the lack of lactation reflex normally induced by suckling has been suggested as a reason but no plausible explanation has been provided by the Applicant regarding the possibility for eplivanserin to affect the mammary gland function. This is a relevant issue that might impact on the use of eplivanserin by e.g. lactating women and should be clarified. The Applicant should propose a strategy to clarify this aspect, clinically or nonclinically.

A revision of pregnancy outcomes in patients treated with molecules with 5HT2A activity has been revised as requested. Though not extensive, no major concerns are raised regarding teratogenicity. The information will be included in the 4.6 section of the SPC.

Eplivanserin did not show any phototoxic or photoallergic effects in the guinea pig, and did not induce any modification of the immune function in rats and baboons.

Environmental Risk Assessment: In Phase I, based on the highest recommended daily dose of 5 mg, a worst-case PEC in surface water (PECsw) of 0.025 µg/L is calculated using default values. Instead, the Applicant obtained a PECsw value (0.0033 µg/L) lower than the 0.01 µg/L action limit and claimed exemption from conducting a Phase II analysis. This PECsw value was calculated using a refined Fpen. The refinement of Fpen was based on internal market research and forecast which contrast with published epidemiology rates of chronic insomnia (ranged from 7.5% to 17.5%) and for maintenance insomnia (ranged from 7.4% to 31.6%) in European and American adults. Thus, a lower prevalence (4.6%) of chronic insomnia with sleep maintenance disorders in the subgroup of population aged over 18 (381 million) was used by the Applicant based on its research. This target patient population was reduced to only 0.33% of that subgroup of adults by considering that only 1.24 million patients would be treated with eplivanserin (diagnose and prescription rate). In addition a compliance rate (180 days/year) was applied to reduce even more the predicted eplivanserin yearly consumption.

The physicochemical properties of eplivanserin include high solubility in water and indicate that ionizable species may occur in the aquatic environment (pKa around 9). The partition coefficient data (log kow lower than 3.63) indicates low likelihood to bioconcentrate. Fate data do not indicate rapid depletion by aerobic biodegradation in wastewater treatment facilities, therefore eplivanserin is not readily biodegradable. However a water sediment study to conclude on the substance fate was not performed. Beside acute toxicity tests (Daphnids and Fathead minnow) and the Algae growth inhibition test no further environmental risk assessment evaluation was performed. In conclusion, this environmental risk assessment suggests that eplivanserin might not cause significant environmental impact following its prescribed use in patients but the risk assessment is not complete and a phase II analysis as per the CHMP ERA guideline and some clarifications will be asked to the Applicant before taking any conclusion on risk to the environment derived from the use of eplivanserin.

In conclusion, eplivanserin presented a profile of toxicity which could be seen at low levels with low or no safety margins for aspects as decreased body weight and food consumption, decreased heart rate and increased blood pressure, with no mechanistic explanation provided. In addition, hormone effects e.g. prolactin increase in rodents and disturbance of oestrus cycle were observed. Whether these effects are linked to the mechanism of action, e.g. through (indirect) dopaminergic modulation is not known. Eplivanserin was not genotoxic. In rodents liver tumours were observed which could be related to liver enzyme induction. Reproductive toxicity was evident with embryotoxicity and teratogenicity in rats and rabbits being identified. No phototoxicity, sensitizing potential or immunotoxicity has been identified in the studies performed. Also no potential for dependence or abuse could be seen in the studies performed. In general, most of toxicities identified (with exception of e.g. cardiovascular and body and food consumption) were observed at high multiples of human exposure. No major objection was then identified. Most of the points raised for discussion were cleared and no further nonclinical discussion is needed. However, some issues, despite being cleared nonclinically are identified for further clinical clarification.

III.3 Clinical aspects

III.3.1 Pharmacokinetics

Eplivanserin (also called SR46349, Z/E isomer) is a new synthetic 5-hydroxytryptamine (5-HT) subtype 2 (5-HT2) receptor agonist. The product is intended for chronic use by oral route only. Generally, the pharmacokinetics of eplivanserin is well characterized.

Apart from in vitro studies, the pharmacokinetic documentation for SLIWENS consists of 17 conventional PK studies including a total of 389 subjects (healthy volunteers and patients). Also population PK analysis was performed using sparse data collected during Phase III clinical studies. Subjects were exposed to single dose or repeated dose in the range of 0.1 mg to 80 mg/day up to three weeks.

Different analytical techniques were used throughout the PK development program, mainly different LC-MS –MS technique variants. Each method was validated separately. However, no data regarding cross-validation of these methods are available. This makes comparisons of pharmacokinetic results across studies difficult.

Eplivanserin and its pharmacologically active circulating N-demethyl metabolite, SR141342, were the primary drug-related moieties assessed in plasma during clinical studies. Indeed, SR141342 was found to be the only major metabolite that may partially contribute to the production of 5-HT2A receptor antagonist activity in the central nervous system (CNS) following the administration of eplivanserin, based on the pharmacological intrinsic in vitro and in vivo activity of these metabolites.

Eplivanserin is well absorbed (>70%) after oral administration, and food (high fat meal) does not modify its bioavailability. Eplivanserin is absorbed by passive diffusion, active transport not being involved.

The absolute oral bioavailability of eplivanserin has not been determined. A mean recovery of 92% of the administered radioactivity can be accepted as an indication of a high extent of absorption since the metabolites were mostly originated from Phase I oxidative pathways. The classification of eplivanserin as a high permeability drug substance on the basis of in vitro (Caco2 cells) data is acceptable but insufficient. Primarily the classification should be based on data from a mass balance study, indicating that more than 85-90% of the drug is absorbed. The applicant should discuss the possibility of using this study's results to support that classification.

The influence of food on the bioavailability of eplivanserin has been investigated in numerous studies. No significant influence of food intake on the BA of eplivanserin was evidenced.

The applicant claims that it is not necessary to perform a final bioequivalence study between the to-be-marketed tablet and the one used in Phase 3 clinical trials due to similarity in composition of the two tablets and the similar dissolution profile at pH 1.2.

Overall, eplivanserin's pharmacokinetic profile is characterized by a late tmax, of around 3 to 6 hours for eplivanserin, and of 6 to 8 hours for SR141342. At 5 mg OD, mean steady-state eplivanserin Cmax ranges from 10.3 to 14.2 ng/mL and mean Cmin from 3.56 to 5.85 ng/mL, demonstrating limited fluctuation between peak and trough concentrations. Steady-state SR141342 plasma exposure represented approximately 50% to 70% of that of eplivanserin. At 5 mg OD, the within-subject variability for eplivanserin and SR141342 steady state AUC0-24 was considered as low (15 - 17%) and the total variability was moderate (<47%) as in patients where a moderate total variability was observed.

Binding to plasma proteins is adequately investigated. Eplivanserin and SR141342 are moderately bound to circulating plasma proteins (about 80 %). No saturation is observed at plasma concentrations 1000 fold higher than plasma levels actually observed in clinical situations. Thus, potential for interaction with other drugs highly bound to plasma proteins is unlikely.

Eplivanserin is extensively metabolized by the liver via N-demethylation leading to SR141342, involving CYP3A4 (around 15%), N-oxidation leading to SR122504 involving flavin monoxygenase (FMO), and conjugation (of unchanged compound and of Phase 1 metabolites). CYP1A1, CYP2B6 and CYP2C9 were not significantly involved in the metabolic clearance of eplivanserin. Other polymorphic enzymes such as CYP2D6 and CYP2C19 were not involved in eplivanserin metabolism process. Eplivanserin is mainly eliminated through renal excretion as metabolites. The mean plasma elimination half-lives of eplivanserin and SR141342 after repeated oral administration were close to 50 and 70 hours, respectively.

Eplivanserin steady state was reached between Day 5 and Day 11, with an accumulation ratio close to 2.5. Steady state of SR141342 was reached between Day 10 and Day 21, with an accumulation ratio between 8 and 10.5 (apparently consistent with the longer half-life and the slow rate of formation of SR141342). At steady-state, eplivanserin and SR141342 exposures increased in a dose proportional manner in the range 0.2 to 10 mg. Eplivanserin and SR141342 exhibit dose and time independent pharmacokinetics, thus steady-state pharmacokinetics can be predicted from the pharmacokinetic profile after a single dose.
Inter-individual (<47%) as well as intra-individual (<17%) variability in target population has been estimated from population PK study.

The pharmacokinetics of eplivanserin and SR141342 in insomniac patients is consistent with that in healthy subjects. The sources of intrinsic variability such as gender, age, body weight and race have a limited impact (less than 1.4-fold) in healthy subjects and in insomniac patients. In subjects with mild and moderate hepatic impairment, eplivanserin and SR141342 exposures were 1.2- to 1.6-fold higher as compared with healthy subjects, consistent with the fact that eplivanserin is extensively metabolized. In agreement with the low renal excretion of eplivanserin, only a 1.3-fold increase in eplivanserin exposure was observed in subjects with moderate and severe renal impairment as compared with healthy subjects or insomniac patients with normal renal function, while exposures to SR141342 (which is partially renally excreted) were 1.8-fold higher.

With respect to the population PK model, the effects of age and renal function are uncertain. Reason being: ranges of the covariates not being sufficiently wide; and also that the effect of creatinine clearance may not have been properly incorporated in the model (creatinine clearance was predicted to affect the central volume of the parent drug, V1p/F). Further, the assessment of the model was difficult as goodness-of-fit was not stratified for parent and metabolite, and we are hesitant how well the model fit both entities. In addition, it should be noted that the shrinkage toward the population mean was high for all parameters apart from CL/F for the parent drug and the so called epsilon shrinkage was very high. This means that the use of many of the diagnostic plots is limited (e.g. ETAs versus covariates and all plots involving individual predictions or individual weighted residuals). Therefore, reference to the population PK model in the SPC should not be done.

Pantoprazole, a proton pump inhibitor that elevates gastric pH did not modify eplivanserin and SR141342 exposures. In addition, in vitro, the solubility of eplivanserin was not significantly affected by the presence of aluminium ions, of magnesium ions, of aluminium and magnesium hydroxides and of sucralfate. Nonetheless, it cannot be extrapolated to antacids such as magnesium hydroxides or alginates

Consistent with the low involvement of CYP3A in eplivanserin metabolism, ketoconazole, a potent inhibitor of CYP3A, did not increase eplivanserin and SR141342 exposure. Based on these results, no specific recommendation on coadministration of CYP3A4 inhibitors was provided in the clinical efficacy/safety studies.

CYP3A inducers may reduce exposure to eplivanserin as observed after rifampicin coadministration with a 62% decrease of eplivanserin AUC while no effect on SR141342 AUC was observed.

Eplivanserin and/or its active metabolite, SR141342, had no potential to inhibit CYP enzymes at the intended therapeutic dose of 5 mg OD, consequently in vivo interactions with substrates of these isoenzymes are unlikely. In addition, eplivanserin and SR141342 were not shown to be substrates nor inhibitors of P-glycoprotein (P-gp) mediated transport, hence in vivo interactions with digoxin or other P-gp substrates are not expected.

Eplivanserin is not an inducer of CYP enzymes, based on in vitro investigations. These results are consistent with in vivo data, showing that eplivanserin/SR141342 did not modify the pharmacokinetics of oral contraceptive steroids (levonorgestrel and ethinylestradiol).

III.3.2 Pharmacodynamics

The binding of eplivanserin with central human 5-HT2A receptors and the determination of the dose level of maximum inhibition of [18F]-altanserin binding were assessed in 2 studies (Studies PDY2473 and PDY3055) using PET scan examination in healthy subjects. Eplivanserin pharmacodynamic effects were either activity and/or safety oriented according to the study objectives. Activity related studies included the sleep EEG studies, Studies PDY2171 and PDY3142, which also included psychomotor and cognitive assessments, the above PET studies and the study in experimental anxiety (Study PDY2170). Safety and/or activity related studies included studies with focus on the lack of next-day residual effects in the morning (Study PDY5434) and throughout the day (Study PDY10272), the lack of impact on driving and psychomotor performances (Study PDY10272) as well as the evaluation of eplivanserin potential drug abuse liability (Study PDY10249). The interaction of eplivanserin on the effects of alcohol and lorazepam (Study INT5432) was assessed. Eplivanserin activity was also assessed in Parkinson's disease (Study PDY2658), sleep disorders in fibromyalgic patients (Study ACT5400), OSAHS (Studies DFI3181, DRI3210, LTS3698, and EFC3211), MDD

(Study DRI2623) and Schizophrenia (Study DFI3024), which will not be further described here since clinical development of eplivanserin in these indications was discontinued.

The results of the pharmacodynamic studies conducted to document the pharmacological activity of eplivanserin and to support its safe use in the treatment of insomniac patients showed that:

- in PET studies eplivanserin was shown to penetrate the blood-brain-barrier and to bind to central 5-HT2A receptors;
- eplivanserin modified sleep architecture with a considerable increase of SWS associated with a decrease of Stage 2 while preserving the physiological structure of sleep in healthy subjects. In one study eplivanserin also decreased the episodes of wakefulness. Eplivanserin did not impact REM sleep. The effect of eplivanserin on SWS was immediate after administration of a single dose of 1 mg with no significant dose-effect. In consequence, doses from 1 mg were considered as potentially active for promoting sleep maintenance by decreasing nocturnal wakefulness in insomniac patients;
- Eplivanserin 5 mg differentiated from flurazepam since it did not exhibit next-day residual effects on psychomotor and cognitive performance including memory:
- Eplivanserin 5 mg did not alter driving performance when used by insomniac patients;
- There is a transient potentiation of the effects of alcohol.

Overall, the set of pharmacodynamic studies provide a reasonable characterization of the profile of eplivanserin. It is not extremely comprehensive but is reasonable to expect that the bulk of the characterization of the product is done in the phase II and III trials. The study on cardiac repolarization will be discussed in the safety section of this report.

III.3.3 Clinical efficacy

The clinical development program for supporting the demonstration of the efficacy and safety of eplivanserin 5 mg/day in the treatment of insomnia with sleep maintenance difficulties consists of 5 randomized, double-blind (DB), placebo-controlled, efficacy and safety studies in adult and elderly patients with primary insomnia and sleep maintenance difficulties (number of treated patients = 3065 patients):

• Study ACT5399 was a DB, randomized study designed to investigate the effects of 2 doses of eplivanserin (1 mg/day and 5 mg/day) in comparison with placebo in the treatment of patients with primary insomnia using patients sleep questionnaires over a 4-week treatment period;

• Study EFC6220 was a DB, randomized study designed to demonstrate the efficacy of eplivanserin 5 mg/day in comparison with placebo after 6 weeks of treatment on sleep maintenance insomnia using night polysomnography (NPSG) recordings;

• Study LTE6217 was a DB, randomized study designed to demonstrate the efficacy of eplivanserin 5 mg/day in comparison with placebo on sleep maintenance insomnia using patients sleep questionnaires over a 12-week treatment period;

• Study LTE6262 was a DB, randomized study designed to demonstrate the efficacy of eplivanserin 5 mg/day in comparison with placebo on sleep maintenance insomnia using patients sleep questionnaires over a 12-week treatment period.

The 12 week DB treatment period was followed by a 40-week open-label (OL) extension phase with eplivanserin 5 mg/day;

• Study EFC10480, a DB, randomized study is designed to demonstrate the safety and efficacy of eplivanserin 5 mg/day and lormetazepam in the treatment of sleep maintenance insomnia after 4 weeks of treatment (ongoing at the submission time, the final report was meanwhile submitted for evaluation).

The efficacy and safety of eplivanserin over placebo in the treatment of chronic insomnia characterized by sleep maintenance difficulties were assessed in 4 multinational, randomized, DB, placebo-controlled studies (see Table 1 below).

Table 1 – Clinical studies in patients with insomnia

| Study | Primary Study Objective | Treatment /duration | Number of Patients[1] | | |
			Placebo	Eplivanserin	Total
ACT5399	To assess the effects of eplivanserin 1 mg/day and 5 mg/day in comparison with placebo using patient sleep questionnaire (QoS) after 4 weeks of treatment	eplivanserin 1mg/day and 5 mg/day during 4 weeks	119	114[2] 117[3]	350
EFC6220	To assess the efficacy of eplivanserin 5 mg/day on sleep maintenance using NPSG after 6 weeks of treatment	eplivanserin 5 mg/day during 6 weeks	311	297	608
LTE6217	To assess the efficacy of eplivanserin 5 mg/day on sleep maintenance using patient sleep questionnaire (pr-WASO) after 12 weeks of treatment	eplivanserin 5 mg/day during 12 weeks	345	617	962
LTE6262	To assess the efficacy of eplivanserin 5 mg/day on sleep maintenance using patient sleep questionnaire (pr-WASO) after 12 weeks of treatment	eplivanserin 5 mg/day during 12 weeks followed by 40 weeks of OL extension phase	295	850	1145
Overall			1070	1995	3065

[1] Number of treated patients
[2] patients who received 5 mg/day of eplivanserin
[3] patients who received 1 mg/day of eplivanserin

Objectives of the studies

The objective of the Phase 2 study (ACT5399) was to explore the effects of 2 doses of eplivanserin (1 mg/day and 5 mg/day) in the treatment of chronic insomnia with predominant sleep maintenance difficulties.

The objective of the Phase 3 studies (EFC6220, LTE6217 and LTE6262) was to demonstrate the efficacy of eplivanserin 5 mg/day on sleep maintenance in large populations of patients with chronic primary insomnia over short and long term periods of treatment.

As recommended in the Guidelines for the clinical evaluation of Hypnotic Drugs, 2 complementary methods were used:

- objective methods in sleep laboratory using polysomnography (PSG) to assess the duration of sleep and awakenings (Study EFC6220);
- subjective methods on outpatient basis using daily patient questionnaires to evaluate, patient reported sleep disturbance (Studies ACT5399, LTE6262, and LTE6217).

Design of the studies

All studies were multinational, DB, randomized placebo controlled with treatment duration from 4 weeks to 12 weeks in patients with primary insomnia. In the Study LTE6262 the 12 weeks of DB treatment was followed by a 40-week open label (OL) extension phase during which all patients received eplivanserin 5 mg/day (Table 2).

Table 2 – Description of overall individual study design and plan

	Run in period	DB treatment period	Open label phase	Run out period
ACT5399	1 week with SB placebo on an outpatient basis	4 weeks of DB treatment with a study visit every week (D7, D14, D21 and D28)	NA	7 nights of out patient treatment with SB placebo
EFC6220	• 1week including • 5 nights of outpatient treatment with SB placebo • 2 consecutive nights of PSG recording in sleep laboratory with SB placebo	• 19 nights of outpatient DB treatment • 2 consecutive nights (N20/N21) of PSG in a sleep laboratory with DB treatment • 19 nights of outpatient DB treatment • 2 consecutive nights (N40/N41) of PSG in a sleep laboratory with DB treatment	NA	14 nights of out-patient treatment with SB placebo
LTE6217	1 week with single-blind placebo on an outpatient basis	12 weeks of out patient DB treatment with visits on Days 14, 28, 42, 63, and 84.	NA	14 nights of out-patient treatment with SB placebo

	Run in period	DB treatment period	Open label phase	Run out period
LTE6262	1 week with single-blind placebo on an outpatient basis	12 weeks of out patient DB treatment with visits on Days 14, 28, 42, 63, and 84.	40 weeks of out patient OL eplivanserin treatment with visits at Week 16, 24, 32, 40, 48 and 52.	14 nights of out-patient treatment with SB placebo

Selection of study population

Adult and elderly patients, (aged 18 years up to 70 years in Study ACT5399 and at least 18 years with no upper limit of age in other studies), suffering from primary insomnia according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision (DSM-IV-TR) criteria were included in these studies.

Sleep maintenance difficulties (at least 1 hour of wakefulness after sleep onset) had to occur at least 3 nights per week over the preceding month. Patients had to spend at least 6.5 hours and no more than 9 hours in bed per night, trying to sleep, over the preceding 2 weeks.

In addition to sleep maintenance difficulties, patients had to report insomnia related impairment of daytime functioning (patients had to respond at least "somewhat interfering" at question 3 of the Insomnia Severity Index [ISI]).

Patients with axis I psychiatric disorders (DSM-IV-TR criteria), with insomnia secondary to chronic pain and with other sleep disorders (primary hypersomnia, narcolepsy, breathing related sleep disorder, circadian rhythm disorder, parasomnia and dyssomnia not otherwise specified [NOS]), history of substance abuse or dependence, or life styles that prevents the diagnosis of primary insomnia (night shift work, napping, excessive consumption of xanthine containing beverages) were excluded from studies.

Patients receiving any over-the-counter or prescription sleep medication (including hypnotics, sedatives and anxiolytics), and patients receiving any substance with psychotropic effects or properties known to affect sleep/wake (eg, neuroleptics, morphine/opioid derivatives, sedative antihistamines, stimulants, antidepressants and clonidine) within 1 week prior to screening, could not be included in these studies.

To qualify for randomization after the completion of the run-in period, patients had to confirm predominant sleep maintenance difficulties (ie, mean WASO≥60 minutes and total sleep time (TST) ≤7 hours and ≥3 hours, either measured on patient sleep questionnaire or based on PSG recordings) and no or few difficulties with sleep initiation (ie, mean latency to persistent sleep [LPS]≤30 minutes in all studies except Study ACT5399). The key inclusion criteria in each of the studies are displayed in Table 3 below.

In addition, evidence of sleep apnoea and periodic leg movement syndrome should have been ruled out (based on PSG criteria in Study EFC6220 and on medical history in other studies), standard laboratory tests for haematology and blood chemistry and electrocardiogram (ECG) should have shown no clinically significant abnormalities and urine drug screen (for opiates, cocaine, amphetamine, cannabinoids, barbiturates, phencyclidine, benzodiazepines, methadone and propoxyphene) had to be negative.

Table 3 – Inclusion criteria for each study

Key inclusion criteria	ACT5399	EFC6220	LTE6217	LTE6262
Adult outpatients aged at least 18	+ Upper limit 70 years	+	+	+
Primary insomnia based on DSM-IV-TR criteria	+	+	+	+
Patient has spent at least 6.5 hours and not more than 9.0 hours, in bed, each night, over the preceding 2 weeks	+	+	+	+
Patient must complain of at least 1 hour of wakefulness after sleep onset 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 question 3 of ISI at screening visit and randomization visit.	-	+	+	+

Based on **PSG recordings** during the screening nights (SN1 and SN2) the following criteria must be present
  – Mean WASO: calculated on SN1 and SN2≥60min, and no screening night with period of WASO<45 min
  – TST≤7 hours and ≥3 hours on both screening nights (SN1 and SN2)
  – Mean SOL ≤30min
	-	+	-	-

Based on **patient questionnaire** during the screening periods the following criteria must be present – Mean WASO ≥60min, and no screening night with period of WASO<45 min (2 nights with pr-WASO<45min were acceptable)	Mean WASO ≥30min	-	+	+
– TST≤7 hours and ≥3 hours on 3 worst screening nights	+	-	+	+
– Mean SOL ≤30min during the screen period (one highest SOL value was to be excluded from the calculation of the mean SOL)	-	+	+	+

Primary and secondary efficacy variables
The primary and main secondary efficacy variables which were assessed in the insomnia studies are presented in Table 4 below:

Table 4 – Primary and main secondary variables assessed in insomnia studies

	Primary efficacy variable	Main secondary efficacy variable
ACT5399	- Change from baseline of pr-QoS at Week 4	None was pre-specified
EFC6220	- Change from baseline of PSG-WASO at night N41/N42	• Change from baseline of General Productivity score of the FOSQ at Week 6. • Change from baseline of pr-WASO (mean of daily evaluations) at Week 6.
LTE6217 and LTE6262	- Change from baseline of pr-WASO (mean of daily evaluations) at Week 6 and at Week 12.	• Change from baseline of the 2 new domains extracted from the General Productivity domain of the FOSQ: • Concentration/memory (questions 1&2) • Hobby/work (questions 4&10) • At weeks 6 and 12.

In Phase 3 studies EFC6220, LTE6217 and, LTE6262 the main secondary variable were those assessing the consequences of the treatment of insomnia on daytime functioning. The Functional Outcomes of Sleep Questionnaire (FOSQ), initially designed to measure daytime functioning in patients with sleep apnoea, was selected and more specifically the General Productivity domain of the FOSQ in Study EFC6220, as having shown sensitivity to change in a 4-week phase 2 study in patients with insomnia receiving another 5-HT2A antagonist the Sponsor has in development.

Following additional validation activities of the FOSQ in insomniac patients, two sets of items from the General Productivity domain were selected and pre-specified for the description of the improvement in daytime concentration/memory and hobby/work outcomes (items 1, 2, 4 and 10) in Studies LTE6217 and LTE6262.

Other secondary variables assessed in individual studies are listed below:
• in the Study EFC6220, from PSG recording (other than PSG-WASO), the change from baseline at Night N20/N21 and Night N41/N42 of: PSG-LPS, PSG-Sleep Efficiency, PSG-NAW and also the sleep architecture variable: % of sleep time spent in each stage (1, 2 and 3-4) and during REM;
• from daily assessments from patient's morning questionnaire, the change from baseline at Week 4 (Study ACT5399), Week 6 (Study EFC6220, LTE6217, LTE6262) and Week 12 (Studies LTE6217, LTE6262) of the following parameters: pr-TST, pr-SOL, pr-NAW, QoS nd refreshing Quality of Sleep; for each parameter assessed from the patient's morning questionnaire, the daily evaluations were averaged in Studies LTE6217 and LTE6262 by planned visit timing (2 or 3 weeks) and by week in Study EFC6220;
• the patient global impression (PGI) scale was the instrument used to evaluate the patients' global perception on the effects of the study treatment, rated by patients (analyzed as binary variable) at Week 4 (Study ACT5399), Week 6 (Studies EFC6220, LTE6217, and LTE6262) and Week 12 (Studies LTE6217 and LTE6262), which consisted of 4 questions (aid to sleep, sleep induction, sleep duration and medication strength) with a 3-category codification.

Evaluation of PSG recordings

The scoring of all night PSGs was performed at a central site level. Records were scored blind to study treatment and study night; some were selected semi randomly for double scoring. Screening Night 1 (SN1) and SN2 recordings were read locally at the investigational sites to allow randomization of the patient within a very short period of time. Subsequent night PSG recordings were sent with the SN1 and SN2 PSG recordings for central reading. Only scoring obtained from the central reading site was used for statistical analysis.

The sleep parameters recorded by PSG were measured on 2 consecutive nights and averaged to decrease the first night effects in the sleep laboratory. The PSG recordings were digital and were scored according to Rechtschaffen and Kales criteria.

The PSG sleep parameters were defined in Table 5.

Table 5 – Definition of PSG parameters

Latency to persistent sleep (minutes)	LPS	Measured from lights-out to the first epoch of 20 consecutive non-wake epochs (sleep onset). Calculation: number of epochs from lights-out to the first of 20 consecutive non-wake epochs (sleep onset) divided by two
Total sleep time (minutes)	TST	Duration of REM plus non-REM (Stage 1, Stage 2, Stage ¾) sleep from lights-out to lights-on. Calculation: Number of REM plus non-REM (Stage 1, Stage 2, Stage ¾) epochs from lights-out to lights-on divided by two
Wake time after sleep onset (minutes)	WASO	Measured from sleep onset to lights-on. Calculation: number of wake epochs from sleep onset to lights-on divided by two
Number of awakenings	NAW	Number of periods of awakenings from sleep onset to lights-on. Calculation: number of times after sleep onset where there is a wake entry on the PSG recording of at least 1 minute duration (at least two consecutive wake epochs). Pairs of awakenings must be separated by a Stage 2 or Stage ¾ of non-REM sleep or REM sleep. Note: two wake entries of at least 1 minute separated by Stage 1 sleep are considered as a single awakening.
Awakening duration*		Duration of each awakening greater than 1 minute between persistent sleep and light-on.
Shift to wake*		All transitions after light-out, to wake from Stage 1,2,3 or REM for any duration and at anytime.
Number of small awakening (duration < 1minute)*		Number of all awakenings lasting less than 1 minute between persistent sleep and light-on.

*Supplementary data calculated by the central site level in order to complete CSR result (exploratory post-hoc analyses).

ACT5399

Study ACT5399 was a multinational, randomized, DB, placebo-controlled, patient-reported-outcome study conducted to investigate the effects of 2 doses of eplivanserin (1 mg/day and 5 mg/day) in the treatment of patients with primary insomnia according to DSM-IV criteria with predominant sleep maintenance difficulties (mean pr-WASO≥30 minutes during the screening week).

A total of 350 patients aged 18 to 70 years (229 women, 121 men, mean (±SD) age 48.3 ± 11.9 years) received either eplivanserin 1mg or eplivanserin 5 mg or placebo, daily in the evening, according to a 1:1:1 ratio, during 4 weeks.

After 1 week of single-blind (SB) placebo run-in period, patients received 4 weeks of treatment on an outpatient basis, during which they answered to daily sleep questionnaires and were evaluated by the Investigator on days 7, 14, 21 and 28. Then, patients completed the study with 1 week SB placebo run-out to assess the effect of treatment discontinuation on sleep. The primary efficacy endpoint was the change from baseline for QoS as measured on a 4-point Likert scale (from 1: excellent to 4: poor) from the patient's sleep questionnaire over the last 7 nights of treatment.

Secondary criteria included patient reported sleep parameters (WASO, TST, NAW, and SOL), PGI, Clinical Global Impression (CGI) of the Investigator and refreshing quality of sleep.

The primary analysis results showed no significant difference between the eplivanserin and the placebo groups for QoS after 4 weeks of treatment (LS mean difference from placebo= -0.08 in eplivanserin 1 mg group and LS mean difference from placebo= -0.012 in eplivanserin 5 mg group with Dunnett adjusted p values of 0.468 and 0.234 respectively). The analysis of the secondary endpoints showed that eplivanserin 5 mg/day decreased pr-WASO (LS mean difference= -11:32 min:sec, 95% CI: -20:13 to -2:51), pr-NAW (LS mean difference= -0.46; 95% CI: -0.79 to-0.12) and increased pr-TST (LS mean difference= 12:13; CI: -1.07 to 25.33), as compared with placebo group. Eplivanserin 5 mg/day also improved the Refreshing Quality of Sleep (LS mean difference = -0.15, 95% CI: -0.30 to-0.00) compared with placebo after 4 weeks of treatment. No effect was observed on sleep induction. Eplivanserin 1 mg/day had no significant effect on pr-WASO and refreshing QoS in comparison with placebo.

EFC6220

Study EFC6220 was a multinational, randomized, DB, placebo-controlled, PSG study aimed at evaluating the efficacy and safety of eplivanserin 5 mg administered daily during 6 weeks, in adult

patients suffering from primary insomnia (DSM-IV-TR criteria) with predominant sleep maintenance difficulties (mean PSG-WASO≥60 minutes at baseline).

A total of 608 patients aged 18 years and above (335 women, 273 men; mean (±SD) age 52.7 ± 14.3 years) were randomized and received either eplivanserin 5 mg or placebo on a 1:1 ratio. The study treatment period was completed by 269 patients (90.6%) in the eplivanserin group and 290 patients (93.2%) in the placebo group. After 1 week SB placebo run-in period, including 2 consecutive nights in a sleep laboratory for baseline PSG recordings, patients received 6 weeks of nightly treatment on an outpatient basis, during which their sleep was evaluated by PSG recordings in the sleep laboratory on nights N20/N21 and N41/N42. Patients then underwent 2 weeks of SB placebo run-out period to assess the effect of treatment discontinuation on sleep.

The primary efficacy endpoint was the change from baseline for PSG-WASO at 6 weeks and the main secondary endpoints were the change from baseline for the score of the General Productivity domain of the FOSQ and the change from baseline for pr-WASO at 6 weeks. Additional secondary endpoints included other PSG sleep parameters, patient-reported-sleep parameters, other domains of the FOSQ and sleep specific PGI (PGI-4 items).

The results showed that, after 6 weeks of treatment (N41/N42), eplivanserin 5 mg decreased the mean PSG WASO by -25:43 min:sec compared with -22:06 min:sec with placebo, with no significant difference between treatment groups (LS mean= -3:37 min:sec; 95% CI: -9:42 to 2:28). At 3 weeks (N20/N21), the mean PSG-WASO decreased from baseline by -24:49 min:sec in the eplivanserin group compared with -18:25 min:sec in the placebo group (LS mean difference= -6:25 min:sec; 95% CI: -12:20 to –0:29). At 6 weeks, the analysis of the 2 main secondary endpoints showed no significant difference between treatment groups for the General Productivity domain of the FOSQ (LS mean difference= -0.01; 95% CI= -0.08 to 0.06), and pr-WASO (LS mean difference= -2:43 min:sec; 95% CI= -8:18 to 2:52,) Analyses of other secondary endpoints showed that, compared with placebo, eplivanserin 5 mg decreased the NAW measured by PSG (LS mean change from baseline = -2.91 and -1.09 for eplivanserin and placebo respectively, with LS mean difference from placebo =-1.82; 95% CI: -2.39 to -1.25) and reported by patients (LS mean change from baseline =-0.79 and -0.54 for eplivanserin and placebo respectively, with LS mean difference from placebo =-0.25, (95% CI: -0.43 to -0.08) after 6 weeks of treatment. In addition, compared with placebo, eplivanserin improved the QoS (LS mean change from baseline = -0.49 and -0.41 for eplivanserin and placebo respectively, with LS mean difference from placebo =-0.09; 95% CI: -0.17 to -0.00) after 6 weeks of treatment).

LTE6217

Study LTE6217 was a multinational, randomized, DB, placebo-controlled, patient reported outcome study aimed at evaluating the efficacy and safety of eplivanserin 5 mg administered daily during 12 weeks, in adult patients suffering from primary insomnia (DSM-IV-TR criteria) with predominant sleep maintenance difficulties (mean pr-WASO≥60 minutes during the screening week).

Nine hundred and sixty two patients aged at least 18 years (548 women, 414 men, mean age 51.2 ± 14.0 years) were randomized in the 12 week DB part of the study and received either eplivanserin 5 mg (617 patients) or placebo (345 patients) according to a 2:1 ratio.

The 12-week treatment period was completed by 485/620 (78.2%) patients in the eplivanserin group and 256/347 (73.8%) patients in the placebo group. The main reason for discontinuation in the eplivanserin group was lack of efficacy (6.9% of patients compared with 11.2% in the placebo group). After 1 week of placebo run-in period, patients received 12 weeks of treatment on an outpatient basis during which they answered daily sleep questionnaires through an IVRS and were evaluated by the Investigator on Days 14, 28, 42, 63, and 84. Patients then underwent 2 weeks of SB placebo run-out period to assess the effect on sleep of treatment discontinuation. The primary efficacy endpoint was the change from baseline for pr-WASO at 12 weeks and the 2 main secondary endpoints were the change from baseline for mean of questions 1&2 (concentration/memory) and questions 4&10 (hobby/work) from the FOSQ, at 12 weeks. Other secondary endpoints included other pr-sleep parameters, FOSQ total score and sub scores of 5 domains, and 4 items of the PGI.

The results showed that eplivanserin 5 mg/day significantly decreased the mean pr-WASO by 54:20min:sec as compared with 42:48min:sec in the placebo group, after 12 weeks of treatment (LS mean difference= -11:32 min:sec, 95% CI: -17:03 to –6:02). The analysis of the 2 main secondary endpoints on FOSQ domains "concentration/memory" (Items 1&2) and "hobby/work" (Items 4&10) did not show any difference between eplivanserin 5 mg/day and placebo at 12 weeks. The analysis of other secondary endpoints showed that eplivanserin decreased the pr-NAW (LS mean change from

baseline = -1.27 and -0.93 for eplivanserin and placebo, respectively, with LS mean difference= -0.33; 95% CI: -0.48 to –0.19), increased the pr-TST (LS mean change from baseline = 49:24 min:sec and 38:28 min:sec for eplivanserin and placebo, respectively, with LS mean difference= 10:56 min:sec; 95% CI: 3:06 to 18:45) and improved the QoS (LS mean change from baseline = -0.73 and -0.62 and for eplivanserin and placebo, respectively, with LS mean difference= -0.10; 95% CI: -0.19 to –0.02) and the Refreshing Quality of Sleep (LS mean change from baseline = -0.70 and -0.60 and for eplivanserin and placebo, respectively, with LS mean difference= -0.09; 95% CI: -0.18 to –0.01) in comparison with placebo after 12 weeks of treatment. No effect was observed on sleep induction.

Comparable results were observed at 6 weeks of treatment. Exploratory analyses conducted to document the onset of action of eplivanserin on sleep maintenance showed that eplivanserin 5 mg/day already decreased pr-WASO from Week 1 (LS mean change from baseline= -28:01 min:sec and -16:42min:sec for eplivanserin and placebo respectively, with LS mean difference= -11:19 min:sec; 95% CI: -15:51 to –6:48). Within Week 1, the results showed that eplivanserin decreased pr-WASO on Day 1 (LS mean change from baseline= -22:03 min:sec and -8:09 min:sec for eplivanserin and placebo respectively, with LS mean difference= -13:54min:sec; 95% CI: -20:29 to -7:19). The sub-group analyses did not detect any interaction between treatment effect and the following factors for pr-WASO: age, gender, race, bodyweight, geographic regions, duration of the current episode of insomnia, previous treatment with sleep medications, and severity of insomnia at baseline and impact of insomnia on daytime functioning as measured on the ISI. The perceived improvement of sleep maintenance and QoS were supported by results of other patient reported outcome measures such as the PGI. Thus, 64.8% of patients from the eplivanserin group versus 52.7% of patients from the placebo group declared that the medication helped them sleep (PGI-item 1; aid to sleep) and 61.1% of patients from the eplivanserin group versus 48.8% of patients from the placebo group declared that the medication lengthened their duration of sleep (PGI-item 3; sleep duration). Finally, 53.9% of patients from the eplivanserin group versus 43.3% of patients from the placebo group declared that the medication strength was "just right" after 12 weeks of treatment.

LTE6262

Study LTE6262 was a multinational, randomized, DB, placebo-controlled, patient reported outcome study aimed at evaluating the efficacy and safety of eplivanserin 5 mg administered daily during 12 weeks, in adult patients suffering from primary insomnia (DSM-IV-TR criteria) with predominant sleep maintenance difficulties (mean pr-WASO≥60 minutes during the screening week, 2 nights with pr-WASO<45min were acceptable).

Study design was similar to that of Study LTE6217, except that there was an extension phase. Patients who completed the 12 week treatment period were offered the opportunity to continue in a 40 week, OL extension phase with eplivanserin 5 mg. Only the results of the DB part of the study are provided in this section.

A total of 1145 patients aged at least 18 years (683 women, 462 men, mean age 51.9years) were randomized in the 12 week DB part of the study and received either eplivanserin 5 mg (850 patients) or placebo (295 patients) according to a 3:1 ratio.

The 12-week treatment period was completed by 676/857 (78.6%) patients in the eplivanserin group and 238/298 (79.9%) patients in the placebo group. The main reason for discontinuation in the eplivanserin and placebo groups was lack of efficacy /disease progression (5.0% and 8.1% respectively). After a 1-week placebo run-in, patients received 12 weeks of treatment on an outpatient basis during which they answered daily sleep questionnaires through an IVRS and were evaluated by the Investigator on Days 14, 28, 42, 63, and 84. The primary efficacy endpoint was the change from baseline for pr-WASO at 12 weeks and the 2 main secondary endpoints were the change from baseline for mean of questions 1&2 (concentration/memory) and questions 4&10 (hobby/work) from the FOSQ, at 12 weeks. Other secondary endpoints included other pr-sleep parameters, FOSQ total score and sub scores for 5 domains, and 4 items from the PGI.

The results showed that eplivanserin 5 mg/day significantly decreased the mean pr-WASO by 53:17 min:sec as compared with 39:46min:sec in the placebo group, after 12 weeks of treatment (LS mean difference= -13:31 min:sec, 95% CI: -19:19 to -7.43). The analysis of the 2 main secondary endpoints on FOSQ domains "concentration/memory" (Items 1&2) and "hobby/work" (Items 4&10) did not show a difference between eplivanserin 5 mg and placebo at 12 weeks with the planned multiple comparison procedure although an improvement related to the domain "hobby/work" was observed in the eplivanserin group (LS mean difference from placebo= 0.10, 95% CI: 0.02 to 0.19). The analysis

of other secondary endpoints after 12 weeks of treatment showed that eplivanserin decreased the pr-NAW (LS mean change from baseline = -1.08 and -0.74 for eplivanserin and placebo, respectively, with LS mean difference= -0.35; 95% CI: -0.50 to -0.19), increased the pr-TST (LS mean change from baseline = 47:10 min:sec and 30:50 min:sec for eplivanserin and placebo, respectively, with LS mean difference= 16:20 min:sec; 95% CI: 9:14 to 23:27) and improved the QoS (LS mean change from baseline = -0.63 and -0.49 for eplivanserin and placebo, respectively, with LS mean difference= -0.14; 95% CI: -0.21 to -0.06) and the Refreshing Quality of Sleep (LS mean change from baseline = -0.60 and -0.45 for eplivanserin and placebo). Exploratory analyses conducted to document the onset of action of eplivanserin on sleep maintenance showed that eplivanserin 5 mg/day decreased pr-WASO as early as the first week of treatment (LS mean change from baseline= -29:00 min:sec and -15:56 min:sec in eplivanserin and placebo groups respectively, with LS mean difference= -13:04 min:sec; 95% CI: -17:52 to –8:16).

Within Week 1, the results showed that eplivanserin decreased pr-WASO on Day 1 (LS mean change from baseline= -19:47 min:sec and -5:05 min:sec in eplivanserin and placebo groups respectively, with LS mean difference= -14:42 min:sec; 95% CI: -22:10 to –7:14). The sub-group analyses did not detect any interaction between treatment effect and the following factors for pr-WASO: age, gender, race, bodyweight, geographic regions, duration of the current episode of insomnia, previous treatment with sleep medications and impact of insomnia on daytime functioning. However, the effect of eplivanserin 5 mg on pr-WASO appeared greater (p = 0.0878) depending on the level of severity of insomnia at baseline as measured on the ISI total score (LS mean differences from placebo= -3:05, -15:34 and -25:45 min:sec for the No/subthreshold, moderate and severe levels, respectively). Thus, 54.5% of patients from the eplivanserin group versus 41.3% of patients from the placebo group declared that the medication helped them sleep (PGI-item 1; aid to sleep) and 50.8% of patients from the eplivanserin group versus 38.3% of patients from the placebo group declared that the medication lengthened their duration of sleep (PGI-item 3; sleep duration,).

No difference between treatment groups was observed regarding anxiety and depression sub scores of the HAD scale after 12 weeks of treatment.

The impact of the treatment of insomnia on health-related work productivity was assessed using the Work Limitation Questionnaire (WLQ), which is a 25-item and 4 dimension scale. The Physical sub-scale covers the ability to perform job tasks that involve bodily strength, movement, endurance, coordination and flexibility. The Mental Interpersonal sub-scale pertains to difficulty performing cognitive tasks and social interactions on-the-job. The Time sub-scale addresses difficulty a job's time and scheduling demands. And finally, the Output sub-scale evaluates the ability to meet demands for quantity, quality and timelines of completed work. The results of the analysis showed that after 12 weeks of treatment eplivanserin 5 mg/day decreased (improved) the Productivity Loss score and 3 out of 4 sub scores related to Time Management, Mental Interpersonal and Output scale. Physical scale score was not impacted.

Pooled data

Study EFC6220- PSG endpoints

The results for the PSG parameters in study EFC6220 are presented in Table 3 below:

Table 3 – PSG parameters at Week 3 and 6-ITT population

		Placebo LS Mean (SEM)	Eplivanserin 5 mg/day LS Mean (SEM)	Difference from Placebo		
				LS Mean	95% Confidence Interval	p-value
PSG-WASO	Week 3	-18:25 (2:07)	-24:49 (2:09)	-6:25	(-12:20 to -0:29)	0.0343
	Week 6	-22:06 (2:10)	-25:43 (2:13)	-3:37	(-9:42 to 2:28)	0.2432
PSG-NAW	Week 3	-0.97 (0.19)	-2.72 (0.20)	-1.74	(-2.29 to -1.20)	<.0001
	Week 6	-1.09 (0.20)	-2.91 (0.21)	-1.82	(-2.39 to -1.25)	<.0001
PSG-TST	Week 3	16:08 (2:16)	22:20 (2:17)	6:12	(-0:07 to 12:31)	0.0544
	Week 6	21:07 (2:24)	22:25 (2:27)	1:18	(-5:27 to 8:02)	0.7054
PSG-LPS	Week 3	2:33 (1:09)	1:51 (1:10)	-0:42	(-3:55 to 2:31)	0.6704
	Week 6	1:12 (1:10)	2:15 (1:11)	1:04	(-2:12 to 4:20)	0.5241
PSG- sleep efficency	Week 3	3.36 (0.47)	4.64 (0.48)	1.28	(-0.03 to 2.60)	0.0556
	Week 6	4.40 (0.50)	4.68 (0.51)	0.28	(-1.13 to 1.68)	0.6986

Note: PSG: polysomnography WASO: wake time after sleep onset, TST: total sleep time, NAW: number of awakening, LPS: latency to persistent sleep
N is the number of patients in the ITT population
p-values come from MMRM analysis adjusting for baseline value

Questionnaire data

The results for the questionnaire data for the main efficacy studies are presented in Fig.1-4, Fig. 8-9 and Fig.12-13. The treatment effects on pr-WASO in elderly patients by study are presented in Table 62.

Figure 1 - pr-WASO at Week 6 - Treatment effect (LS mean difference in change from baseline 95%CI) by study and in meta-analysis - ITT population

Figure 2 - pr-WASO at Week 12 - Treatment effect (LS mean difference in change from baseline + 95%CI) by study and in meta-analysis - ITT population

Pr–WASO at week 12

Figure 3 - pr-NAW at Week 6 - Treatment effect (LS mean difference in change from baseline + 95%CI) by study and in meta-analysis - ITT population
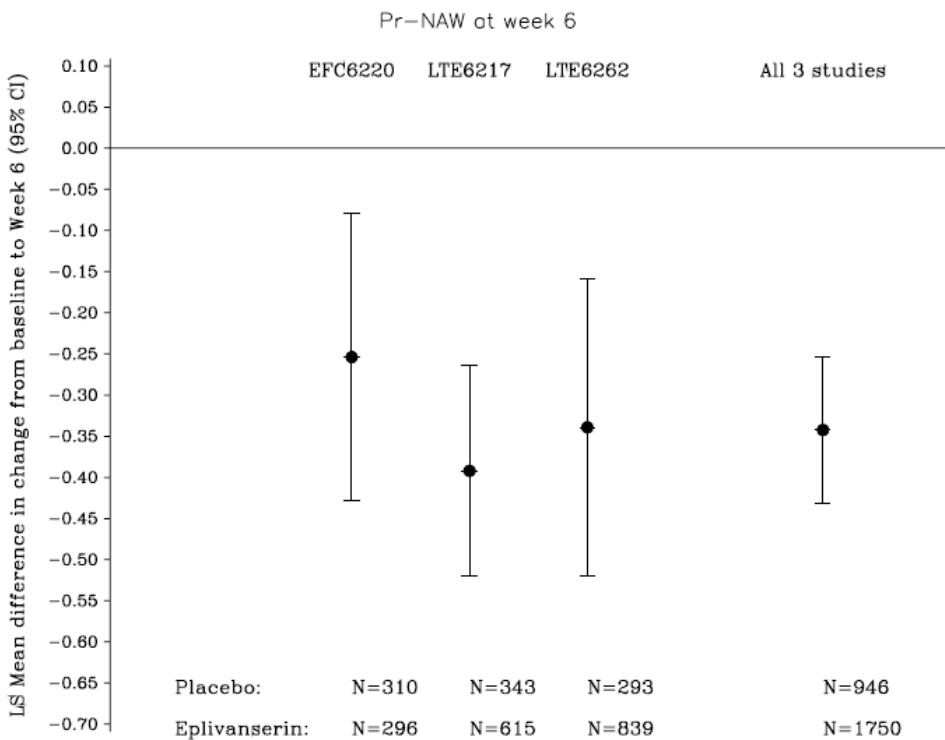
Pr–NAW at week 6

Figure 4 - pr-NAW at Week 12 - Treatment effect (LS mean difference in change from baseline + 95% CI) by study and in meta-analysis - ITT population

Pr—NAW at week 12

LTE6217   LTE6262   All 2 studies

Placebo: N=343   N=293   N=636
Eplivanserin: N=615   N=839   N=1454

Figure 8 - FOSQ Items "concentration/memory" mean - Treatment effect (LS mean difference in change from baseline + 95% CI) by study and in meta-analysis at Week 6 - ITT population

FOSQ: mean of items 1 and 2 concentration/memory at week 6

EFC6220   LTE6217   LTE6262   All 3 studies

Placebo: N=297   N=329   N=276   N=902
Eplivanserin: N=288   N=592   N=809   N=1689
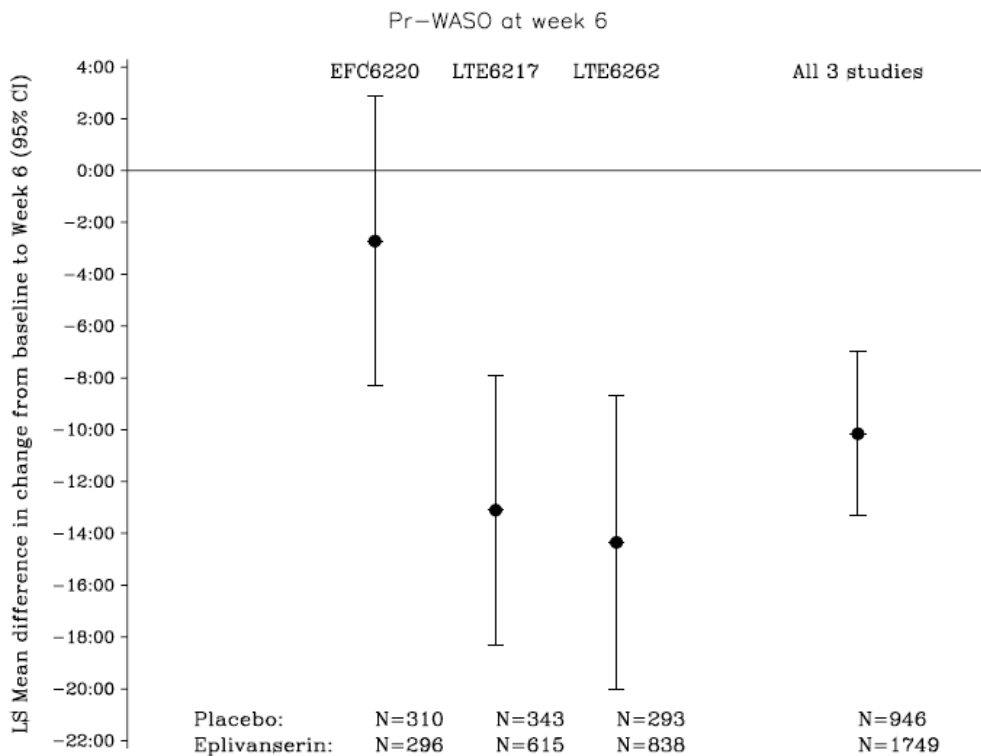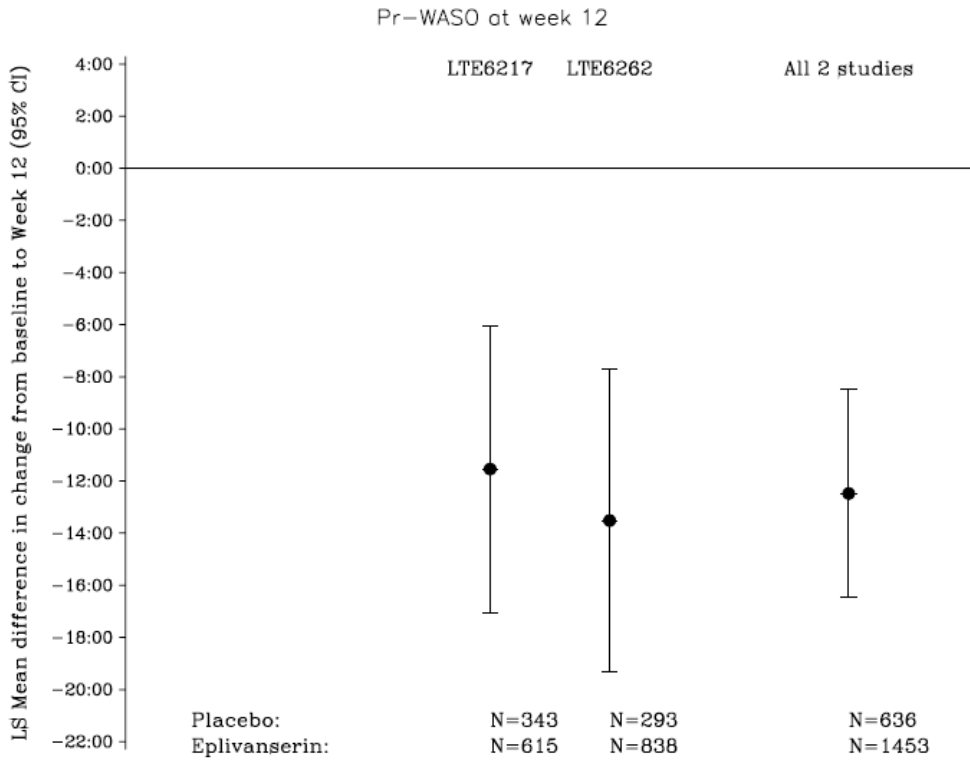
Figure 9 - FOSQ Items "concentration/memory" mean - Treatment effect (LS mean difference in change from baseline + 95% CI) by study and in meta-analysis at Week 12 - ITT population

FOSQ: mean of items 1 and 2 concentration/memory at week 12

Figure 12 - pr-WASO (min:sec) in subpopulations at Week 6 (Pool 3 studies)

	# pts	est(low to high)
Overall	2694	-11:14 (-14:23 to -8:04)
Sex (p-value* : 0.7633)		
Male	1139	-10:37 (-15:24 to -5:50)
Female	1555	-11:35 (-15:43 to -7:26)
Age (p-value* : 0.3983)		
<65	2217	-10:44 (-14:11 to -7:16)
>=65	477	-14:14 (-21:37 to -6:50)
Race (p-value* : 0.2150)		
Caucasian	2399	-12:09 (-15:30 to -8:48)
Black	165	-7:11 (-19:24 to 5:02)
Other	130	-0:31 (-14:13 to 13:12)
Geogr. region (p-value* : 0.1371)		
US	1278	-8:29 (-12:58 to -4:00)
Europe	766	-16:03 (-22:02 to -10:03)
Rest of the world	650	-10:21 (-16:50 to -3:52)
Weight (p-value* : 0.2892)		
<75	1462	-12:46 (-17:03 to -8:29)
>=75	1232	-9:23 (-14:00 to -4:46)
Current ep. dur. (p-value* : 0.7439)		
<=5	1202	-9:35 (-14:21 to -4:49)
]5-10]	527	-12:11 (-19:09 to -5:13)
>10	962	-11:59 (-17:09 to -6:48)
ISI tot score (p-value* : 0.8375)		
No/Subthreshold	698	-9:55 (-15:58 to -3:53)
Moderate	1666	-11:47 (-15:47 to -7:47)
Severe	324	-9:42 (-18:47 to -0:36)
ISI int. daily liv (p-value* : 0.9801)		
No/A little int.	1118	-10:45 (-15:34 to -5:56)
Much	1171	-11:21 (-16:07 to -6:35)
Very much	399	-10:36 (-18:47 to -2:25)
Prev. sleep med (p-value* : 0.4752)		
No	1834	-10:26 (-14:14 to -6:39)
Yes	860	-12:53 (-18:29 to -7:18)

Estimate and 95 pct IC (minutes)

Figure 13 - pr-WASO (min:sec) in subpopulations at Week 12 (Pool 2 studies)

	# pts	est(low to high)
Overall	2089	-12:19 (-16:18 to -8:19)
Sex (p-value* : 0.7287)		
Male	867	-11:26 (-17:35 to -5:17)
Female	1222	-12:52 (-18:05 to -7:38)
Age (p-value* : 0.4967)		
<65	1750	-11:51 (-16:11 to -7:31)
>=65	339	-15:38 (-25:38 to -5:37)
Race (p-value* : 0.5666)		
Caucasian	1940	-12:09 (-16:17 to -8:00)
Black	99	-19:04 (-37:41 to -0:26)
Other	50	-1:09 (-28:48 to 26:30)
Geogr. region (p-value* : 0.9337)		
US	804	-12:29 (-18:58 to -5:59)
Europe	766	-11:29 (-17:57 to -5:02)
Rest of the world	519	-13:26 (-21:34 to -5:17)
Weight (p-value* : 0.5718)		
<75	1151	-13:20 (-18:42 to -7:58)
>=75	938	-11:01 (-16:59 to -5:04)
Current ep. dur. (p-value* : 0.4102)		
<=5	949	-11:42 (-17:45 to -5:39)
]5-10]	398	-17:01 (-25:53 to -8:08)
>10	740	-9:31 (-16:07 to -2:56)
ISI tot score (p-value* : 0.5211)		
No/Subthreshold	524	-8:35 (-16:23 to -0:47)
Moderate	1320	-13:18 (-18:20 to -8:17)
Severe	239	-15:34 (-27:48 to -3:20)
ISI int. daily liv (p-value* : 0.3793)		
No/A little int.	818	-11:52 (-18:10 to -5:34)
Much	947	-10:22 (-16:19 to -4:26)
Very much	318	-18:50 (-29:15 to -8:26)
Prev. sleep med (p-value* : 0.8498)		
No	1403	-12:02 (-16:52 to -7:12)
Yes	686	-12:51 (-19:54 to -5:48)

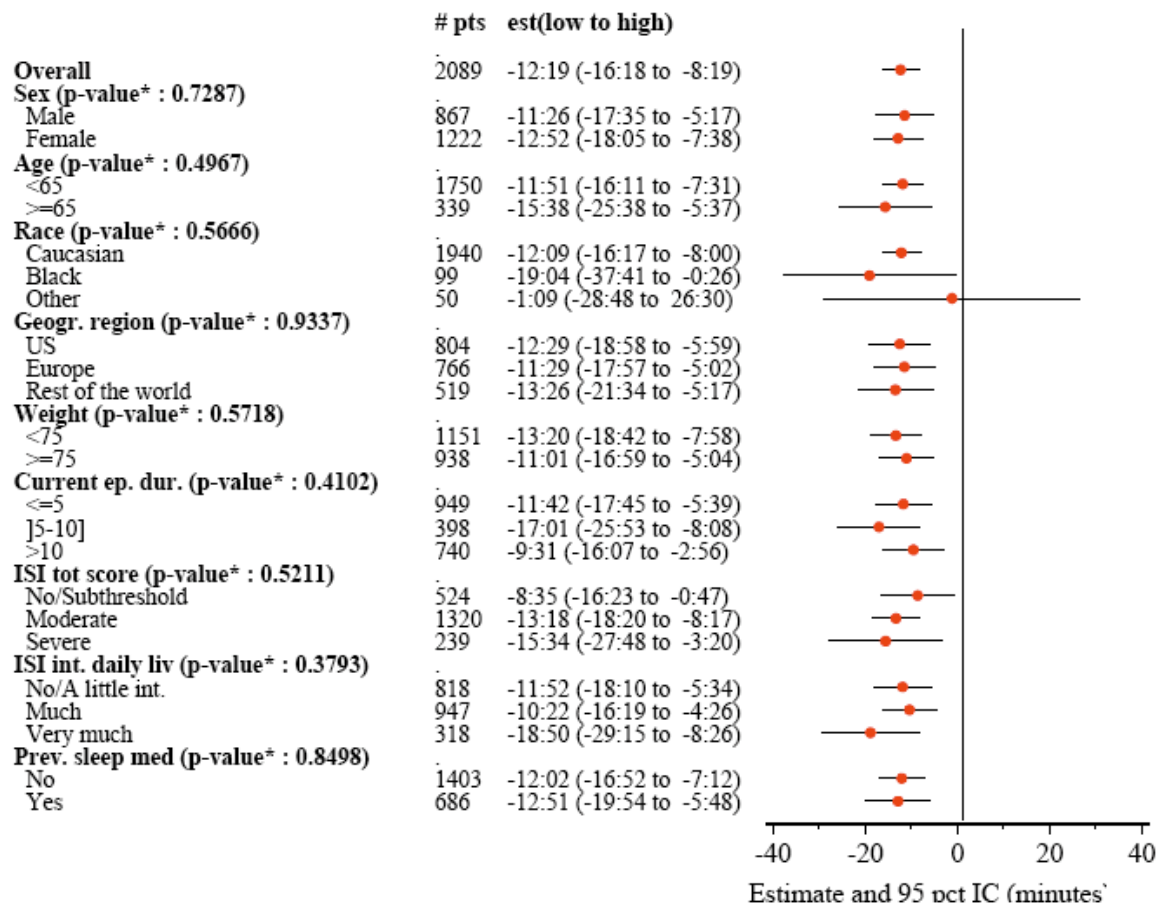Estimate and 95 pct IC (minutes)

Table 62 - Treatment effect of pr-WASO in elderly patients - By study – ITT population

	Studies		Placebo	Eplivanserin 5 mg/day
pr-WASO 4 weeks	ACT5399	Number	11	9
		LS Mean (SEM)	-17:51 (10:54)	-16:04 (12:05)
		LS Mean Diff from Placebo (SEM)		1:47 (16:24)
		95% Confidence Interval		(-31:46 to 35:21)
		p-value vs Placebo		0.9138
pr-WASO 6 weeks	EFC6220	Number	69	70
		LS Mean (SEM)	-11:59 (4:34)	-24:31 (4:33)
		LS Mean Diff from Placebo (SEM)		-12:32 (6:27)
		95% Confidence Interval		(-25:18 to 0:14)
		p-value vs Placebo		0.0542
	LTE6217	Number	57	110
		LS Mean (SEM)	-24:28 (5:22)	-42:55 (3:48)
		LS Mean Diff from Placebo (SEM)		-18:27 (6:35)
		95% Confidence Interval		(-31:27 to -5:26)
		p-value vs Placebo		0.0058
	LTE6262	Number	41	131
		LS Mean (SEM)	-35:58 (8:06)	-45:36 (4:28)
		LS Mean Diff from Placebo (SEM)		-9:38 (9:16)
		95% Confidence Interval		(-27:57 to 8:41)
		p-value vs Placebo		0.3009
	Meta-analysis 3 studies	Number	167	311
		Diff from Placebo (SEM)		-14:17 (4:08)
		95% Confidence Interval		(-22:22 to -6:11)
		p-value vs Placebo		0.0005
pr-WASO 12 weeks	LTE6217	Number	57	110
		LS Mean (SEM)	-30:35 (5:41)	-45:25 (4:01)
		LS Mean Diff from Placebo (SEM)		-14:51 (6:58)
		95% Confidence Interval		(-28:37 to -1:05)
		p-value vs Placebo		0.0348
	LTE6262	Number	41	131
		LS Mean (SEM)	-35:58 (8:17)	-53:19 (4:33)
		LS Mean Diff from Placebo (SEM)		-17:21 (9:29)
		95% Confidence Interval		(-36:04 to 1:23)
		p-value vs Placebo		0.0691
	Meta-analysis 2 studies	Number	98	241
		Diff from Placebo (SEM)		-15:43 (5:37)
		95% Confidence Interval		(-26:43 to -4:43)
		p-value vs Placebo		0.0051

Note: pr-WASO : patient reported wake time after sleep onset
Number is the number of patients for the given parameter with no missing data, baseline value is used as a covariate in MMRM analysis
PGM=SR46349/OVERALL/SUB_2008/BS/PGM_RPT/CSE_mmrmprwaso_ge65.sas OUT=OUTPUT/CSE_mmrmprwaso_ge65.rtf (03OCT2008 - 11:14)

EFC10480 - Comparison of the safety and efficacy of eplivanserin and lormetazepam in the treatment of insomnia characterized by sleep maintenance difficulties. A 4 week, randomized, double-blind, comparative, parallel group study.

Objectives:
Primary
• To compare the potential for next-day residual effects of eplivanserin 5 mg/day and lormetazepam 1 mg/day by measuring the sleepiness in the morning using the patient's sleep questionnaire during 4 weeks of treatment in patients with chronic primary insomnia and sleep maintenance difficulties.
Secondary
• To compare the clinical safety of both products, including the potential for rebound insomnia and withdrawal symptoms after treatment discontinuation.
• To compare the efficacy of both products on subjective sleep parameters (patient reported (pr)-Wake time After Sleep Onset (WASO), pr-Total Sleep Time (TST), pr-Number of Awakenings (NAW), pr-Sleep Onset Latency (SOL), Quality of Sleep (QoS), refreshing QoS).
• To compare the effects of both products on patient's daytime functioning using the Functional Outcome Sleep Questionnaire (FOSQ) and the Sleep Impact Scale (SIS) after 4 weeks of treatment.

Methodology: International, multicenter, phase III, randomized, double-blind, comparative study, with two parallel groups.

Number of patients: Planned: 266 (133 per group); Randomized: 283 (140 eplivanserin group) and 143 (lormetazepam group); Treated: 283 (140 eplivanserin group) and 143 (lormetazepam group).

Evaluated: Efficacy: 278 (137 eplivanserin group) and 141 (lormetazepam group) Safety: 283 (140 eplivanserin group) and 143 (lormetazepam group); Pharmacokinetics: Pharmacokinetics were not assessed in this study.

Diagnosis and criteria for inclusion:
Outpatients, aged 18 years and above with primary insomnia according to DSM-IV-TR criteria. The patient must have complained of at least 1 hour of wakefulness for at least 3 nights per week during the preceding month. The patient must have spent at least 6.5 hours and not more than 9 hours in bed (time in bed = TIB) trying to sleep, each night during the preceding 2 weeks.
Based on patient's sleep questionnaire administered each morning during the run-in period, patients must have had the following (calculated on at least 4 nights):
• a mean pr-WASO ≥45 min,
• a mean pr-TST <7 hours and >3 hours,
• a mean pr-SOL ≤30 min.

Patients' characteristics: A total of 413 patients were screened, of whom 283 patients were randomized. The main reason for non-randomization was "inclusion/exclusion criteria not respected" (28.6%). Both treatment groups were comparable regarding demographic data. The median age of patients was 52.0 years and 12.4% of patients were elderly (≥65 years).
Two third of patients were female. More than 85% of patients were non Hispanic. The mean time from first diagnosis of primary insomnia was 7.25 years and 6.56 years in the eplivanserin and the lormetazepam group, respectively. In about 80% of patients the time from first diagnosis to randomization was more than 1 year, reaching 10 years in 68/283 (24.3%) patients.

Results
The results for study EFC10480 are summarised in Tables 37-42 below.

Table 37 – pr-WASO (min:sec) change from baseline at week 4 (MMRM analysis) - ITT population

	Eplivanserin 5mg/day (N=137)	Lormetazepam 1mg/day (N=141)
Number	137	141
Baseline		
Mean (SD)	86:39 (42:17)	82:41 (41:11)
Median	70:00	67:30
Q1 ; Q3	56:26 ; 102:51	50:20 ; 99:17
Min ; Max	30:00 ; 222:51	31:15 ; 255:00

	Eplivanserin 5mg/day (N=137)	Lormetazepam 1mg/day (N=141)
Change from baseline at week 4		
LS Mean (SEM)	-37:09 (2:56)	-45:12 (2:52)
LS Mean Difference from Lormetazepam 1mg/day (SEM)	8:04 (4:06)	
95% Confidence Interval	(-0:02 to 16:09)	
p-value vs. Lormetazepam 1mg/day	0.0511	

Note : pr-WASO : patient reported wake time after sleep onset
Number refers to patients for the given parameter with baseline and post-baseline values.
Estimations and p-value based on a Repeated Measurement Model with baseline as covariate
PGM=SR46349/EFC10480/CSR/BS/PGM_RPT/I26_mmrmprwaso.sas OUT=OUTPUT/I26_mmrmprwaso_i.rtf (16APR2009 - 16:26)

Table 38 – pr-TST (min:sec) change from baseline at week 4 (MMRM analysis) - ITT population

	Eplivanserin 5mg/day (N=137)	Lormetazepam 1mg/day (N=141)
Number	137	141
Baseline		
Mean (SD)	342:16 (46:17)	338:41 (52:10)
Median	347:30	351:00
Q1 ; Q3	317:51 ; 377:30	304:17 ; 380:00
Min ; Max	167:09 ; 419:17	180:00 ; 422:30

	Eplivanserin 5mg/day (N=137)	Lormetazepam 1mg/day (N=141)
Change from baseline at week 4		
LS Mean (SEM)	34:31 (4:31)	55:03 (4:25)
LS Mean Difference from Lormetazepam 1mg/day (SEM)	-20:33 (6:19)	
95% Confidence Interval	(-33:00 to -8:05)	
p-value vs. Lormetazepam 1mg/day	0.0013	

Note : pr: patient reported, TST: total sleep time
Number refers to patients for the given parameter with baseline and post-baseline values.
Estimations and p-value based on a Repeated Measurement Model with baseline as covariate
PGM=SR46349/EFC10480/CSR/BS/PGM_RPT/I26_mmrmprtst.sas OUT=OUTPUT/I26_mmrmprtst_i.rtf (16APR2009 - 16:26)

Table 39 – pr-NAW change from baseline at week 4 (MMRM analysis) - ITT population

	Eplivanserin 5mg/day (N=137)	Lormetazepam 1mg/day (N=141)
Number	137	141
Baseline		
Mean (SD)	2.82 (1.76)	2.53 (1.08)
Median	2.38	2.33
Q1 ; Q3	1.7 ; 3.4	1.8 ; 3.3
Min ; Max	0.8 ; 10.9	0.6 ; 5.1
Change from baseline at week 4		
LS Mean (SEM)	-1.10 (0.10)	-1.01 (0.10)
LS Mean Difference from Lormetazepam 1mg/day (SEM)	-0.09 (0.14)	
95% Confidence Interval	(-0.36 to 0.19)	
p-value vs. Lormetazepam 1mg/day	0.5251	

Table 40 – pr-SOL (min:sec) change from baseline at week 4 (MMRM analysis) - ITT population

	Eplivanserin 5mg/day (N=137)	Lormetazepam 1mg/day (N=141)
Number	137	141
Baseline		
Mean (SD)	19:05 (8:17)	19:19 (8:36)
Median	19:10	19:10
Q1 ; Q3	13:08 ; 25:00	13:34 ; 25:43
Min ; Max	4:09 ; 62:09	2:09 ; 62:09
Change from baseline at week 4		
LS Mean (SEM)	5:42 (1:51)	1:02 (1:48)
LS Mean Difference from Lormetazepam 1mg/day (SEM)	4:39 (2:34)	
95% Confidence Interval	(-0:25 to 9:43)	
p-value vs. Lormetazepam 1mg/day	0.0716	

Note : pr: patient reported, SOL: Sleep Onset Latency
Number refers to patients for the given parameter with baseline and post-baseline values.
Estimations and p-value based on a Repeated Measurement Model with baseline as covariate
PGM=SR46349/EFC10480/CSR/BS/PGM_RPT/I26_mmrmprsol.sas OUT=OUTPUT/I26_mmrmprsol_i.rtf (16APR2009 - 16:26)

Table 41 – QoS change from baseline at week 4 (MMRM analysis) - ITT population

	Eplivanserin 5mg/day (N=137)	Lormetazepam 1mg/day (N=141)
Number	137	141
Baseline		
Mean (SD)	3.19 (0.46)	3.18 (0.47)
Median	3.17	3.14
Q1 ; Q3	2.9 ; 3.5	2.9 ; 3.4
Min ; Max	2.0 ; 4.0	1.9 ; 4.0

	Eplivanserin 5mg/day (N=137)	Lormetazepam 1mg/day (N=141)
Change from baseline at week 4		
LS Mean (SEM)	-0.59 (0.05)	-0.63 (0.04)
LS Mean Difference from Lormetazepam 1mg/day (SEM)	0.04 (0.06)	
95% Confidence Interval	(-0.09 to 0.16)	
p-value vs. Lormetazepam 1mg/day	0.5614	

Sleep quality ranging from 1 (excellent) to 4 (poor)
Number refers to patients for the given parameter with baseline and post-baseline values.
Estimations and p-value based on a Repeated Measurement Model with baseline as covariate
PGM=SR46349/EFC10480/CSR/BS/PGM_RPT/I26_mmrmprsldes.sas OUT=OUTPUT/I26_mmrmprsldes_i.rtf (01JUL2009 - 11:37)

Table 42 – Refreshing QoS change from baseline at week 4 (MMRM analysis) - ITT population

	Eplivanserin 5mg/day (N=137)	Lormetazepam 1mg/day (N=141)
Number	137	141
Baseline		
Mean (SD)	3.17 (0.47)	3.18 (0.48)
Median	3.14	3.14
Q1 ; Q3	2.9 ; 3.4	2.8 ; 3.6
Min ; Max	2.0 ; 4.0	2.1 ; 4.0
Change from baseline at week 4		
LS Mean (SEM)	-0.60 (0.04)	-0.62 (0.04)
LS Mean Difference from Lormetazepam 1mg/day (SEM)	0.02 (0.06)	
95% Confidence Interval	(-0.10 to 0.15)	
p-value vs. Lormetazepam 1mg/day	0.7138	

Sleep refreshing quality ranging from 1 (excellent) to 4 (poor)
Number refers to patients for the given parameter with baseline and post-baseline values.
Estimations and p-value based on a Repeated Measurement Model with baseline as covariate
PGM=SR46349/EFC10480/CSR/BS/PGM_RPT/I26_mmrmprslref.sas OUT=OUTPUT/I26_mmrmprslref_i.rtf (01JUL2009 - 11:37)

III.3.4 Clinical safety

As of March 12, 2008, all of the 2948 insomniac patients who were enrolled in the 4 DB, randomized, placebo-controlled studies in insomnia and received at least 1 dose of study drug (placebo: 1070 and eplivanserin 5 mg: 1878) were evaluated for safety. Throughout the clinical development of eplivanserin, the safety was routinely monitored by spontaneous reporting of adverse events (AEs), regular physical examinations and evaluations of clinical laboratory data, measurements of vital signs and recordings of ECGs.

Specific safety evaluations related to the use of sleep medications (eg, measure of next-day residual effects, assessment of rebound insomnia and withdrawal after treatment discontinuation, and drug abuse potential) were performed. These specific safety considerations were addressed not only in patients with insomnia but also in healthy subjects and in recreational drug users in clinical pharmacology studies. Next-day residual effects were measured in patients both objectively using psychometric tests (DSST for alertness and RAVLT for memory) and subjectively on patient reported outcomes (sleepiness in the morning and ability to concentrate) collected on daily sleep questionnaires. In clinical pharmacology studies, next-day residual effects were assessed using a battery of psychometric tests for neurocognitive and psychomotor performances, including memory. Potential for rebound insomnia was measured on patient-reported sleep parameters, and values after treatment discontinuation were compared with baseline values. Potential for withdrawal effects was measured in patients on the Physician Withdrawal Checklist (PWC) which is a scale initially designed to assess benzodiazepine discontinuation symptoms and on the spontaneously reported AEs during the treatment discontinuation periods. Finally, abuse potential was explored by specific clusters of adverse events reported during the course of the clinical studies.

Additional data from Phase 2 trials conducted in other indications than insomnia (ie, schizophrenia, MDD, AD, OSAHS and fibromylagia) was analyzed.

Definition of clinical trial patient populations

The primary safety population (Pool 1) for the evaluation of the safety of eplivanserin 5 mg in the proposed indication corresponds to insomniac patients included in the 4 DB randomized placebo-controlled study (Studies ACT5399, EFC6220, LTE6217, and LTE6262). This pool did not include patients from Study ACT5399 having received eplivanserin 1 mg. Among the 2948 patients, 501 patients were aged ≥65 years. Two other pools were part of the integrated safety data base. Pool 2 that included data from Pool 1, the 1 mg data from Study ACT5399 and data from Phase 2 placebo-controlled studies in other indications. This pool aimed mainly at the determination of the adverse event profile of sub-therapeutic doses of eplivanserin and was used for the drug abuse liability assessment. Pool 3 included all eplivanserin 5 mg data from Pool 2 (DB period) and from the open label extension period of Study LTE6262. This pool gathered all safety data with eplivanserin 5 mg including the long-term safety data.

In Pool 1, a total of 1858 insomniac patients (among whom 322 patients were ≥65 years and 77 patients were aged ≥75 years) were exposed to eplivanserin 5 mg with mean treatment duration of about 67 days (59 in the placebo group. A total of 530 patients were exposed between 6 and 12 months and 119 for at least 12 months.

Common adverse drug reactions

A relative risk analysis was performed as the main analysis to determine differences considered significant between eplivanserin 5 mg and placebo regarding the High Level Term (HLT) reported adverse events. A relative risk (RR) ratio>1 and a lower bound ≥0.8 for the RR Confidence Interval were selected for a meaningful and broad evaluation of the AE profile. Then, relevant subordinate Preferred Terms (PT≥1%) were considered clinically meaningful when a ≥0.5% difference between eplivanserin and placebo was observed.

Based on this analysis and taking into account the difference of exposure between groups, the commonly reported (in ≥1% patients) adverse drug reactions (ADR) during treatment with eplivanserin 5 mg/day for 4 weeks to 12 weeks in patients with insomnia, were: dizziness (4.9% versus 3.2% with placebo), dry mouth (3.6% versus 1.1% with placebo), diarrhoea (3.2% versus 2.1% with placebo), abdominal pains (including abdominal pain upper, abdominal pain, abdominal pain lower and abdominal tenderness) (2.3% versus 0.9% with placebo), constipation (1.8% versus 0.8% with placebo), diverticulitis (1.2% versus 0% with placebo), and pharyngolaryngeal pain (1% versus 0.5% with placebo).

In addition to the main RR analysis, a thorough search for clinically relevant ADRs when grouping some related terms was performed. It allowed the identification of a significant difference between eplivanserin 5 mg and placebo (1.2% versus 0.3%) for skin reactions (grouping of rash-related terms: rash, rash maculopapular, rash pruritic, and erythema).

Dizziness was the most frequently reported TEAE in patients (4.9% versus 3.2% with placebo) in insomniac patients who received eplivanserin 5 mg.

Adverse events of specific interest

During the Phase 2-3 clinical development program of eplivanserin, at the cut-off date of 19 June 2008, a total of 30 cases of patients presenting diverticulitis were reported in the 3030 eplivanserin-treated patients versus none with placebo.

A total of 39 episodes of diverticulitis were reported for the 30 patients. The majority of the patients had a single episode of diverticulitis (23/30). The number of episodes of diverticulitis, per patient, varied from 1 to 4. One patient had 4 episodes and 6 patients had 2 episodes. In 5 of the 7 patients who experienced recurrent diverticulitis episodes, a medical history of diverticular disease/divericulitis was reported. Three out of the 39 episodes of diverticulitis were reported of mild intensity, 26/39 of moderate intensity and 10/39 of severe intensity.

Withdrawals due to adverse events

The incidence of patients who discontinued treatment due to adverse events was low but higher in eplivanserin 5 mg group than in placebo (4.5% versus 2.7%). The most frequent AEs leading to treatment discontinuation in the eplivanserin 5 mg group were from the following SOCs: nervous system disorders (1.4% versus 1.1% in placebo group) mainly dizziness (0.4% versus <0.1%) and somnolence (0.4% versus 0.2%), and psychiatric disorders (0.8% versus 0.4%) mainly depression (0.2% in each group) and anxiety (0.2% versus <0.1%).

Serious adverse events
Overall in patients with insomnia, serious TEAEs were reported in 1.8% of patients in the eplivanserin 5 mg group compared with 0.9% in placebo. The most frequent SAEs were reported in the following SOCs: infections and infestations (0.5% versus 0.3%), general disorders and administration site conditions (0.3% versus none) and injury, poisoning and procedural complications disorders (0.3% versus <0.1%). The most frequently reported serious TEAEs were diverticulitis (0.3%). Other SAEs could be linked either to underlying diseases or were of various intercurrent origins and were individually reported with a low frequency in each treatment group.

Deaths
During the whole development program with eplivanserin, one case with fatal outcome (right upper lobe mass/possible malignancy coded as lung neoplasm malignant) was reported in a 64-year- old chronic smoker male patient receiving eplivanserin 5 mg for insomnia for 7 weeks.

Vital signs, clinical laboratory data and ECG
Eplivanserin did not modify heart rate (HR), blood pressure (BP) and weight in the global population included in the Phase 2 and 3 studies.
However, in the elderly population, orthostatic hypotension either measured as a potentially clinically significant abnormality (PCSA) or reported as a TEAE (21.1% versus 14.5% with placebo) was noted with eplivanserin 5 mg.

Effects of eplivanserin on clinical laboratory data
In the overall clinical development program, eplivanserin was not associated with significant modifications of standard laboratory parameters evaluating haematology, renal function, liver function and glucose.

Effects of eplivanserin on electrocardiogram
Confirming the results of the specific thorough ECG study, eplivanserin in Phase 2-3 studies was not shown to modify ECG parameters (HR, PR, QRS and QTcF) in the global population.
However, in the elderly population, PCSA of prolonged PR were detected more frequently with eplivanserin than placebo.

Interaction effects
Intrinsic factors
There was no influence of gender, race and renal function on the safety profile of eplivanserin.
In insomniac patients, age was shown to impact the safety profile of eplivanserin 5 mg. Although the adverse events profile remained the same in the elderly (patients ≥65 years old) as in the global population, nasopharyngitis, diverticulitis and oral dryness were reported with a slightly higher incidence in elderly than in the global population.

Extrinsic factors
Based on the pharmacokinetic characteristics of eplivanserin and its active metabolite and on the results of specific pharmacokinetic interaction studies in healthy subjects, no pharmacokinetic drug-drug interaction was expected for eplivanserin. In Phase 2-3 studies, only 14 patients received a CYP3A4 inhibitor concomitantly with eplivanserin. This limited number of patients did not allow the detection of any safety signal.
Due to the activity of 5-HT2A antagonists on platelet aggregation, the safety profile of patients who took both eplivanserin and an oral platelet antiaggregant was evaluated and no safety issue was identified.

Next-day residual effects
In addition to clinical pharmacology studies in healthy subjects and in patients with insomnia performed to evaluate the next-day effects of eplivanserin on cognitive and psychomotor performances, including driving performance, the potential next-day residual effects were also assessed in Phase 2 and 3 studies. In fact the potential next-day residual effects that might be associated with the administration of eplivanserin 5 mg were assessed using psychometric tests in the PSG study (Study EFC6220) and on patient-reported (pr) sleepiness in the morning and on pr-ability to concentrate recorded on sleep questionnaires, every day, during the whole treatment duration in Studies ACT5399, EFC6220, LTE6217, and LTE6262.

In the large population of insomniac patients, no next-day effects was observed as measured by: psychometric tests for alertness and vigilance (DSST) and memory (RAVLT), both in the morning and in the evening, and also measured by using sleep questionnaire for sleepiness in the morning and ability to concentrate. It should be noted that a favorable effect of eplivanserin was observed in comparison with placebo with an improvement of sleepiness in the morning and of ability to concentrate. In the elderly population, except for DSST in the evening, the results did not show meaningful next-day residual effects on the same measurement tools.

Rebound

The potential for rebound of insomnia was assessed in the Phase 2 Study ACT5399 and three Phase 3 studies (Studies EFC6220, LTE6217 and LTE6262) during a run-out period of one-week single-blind (SB) placebo in Study ACT5399 and two weeks SB placebo in Studies EFC6220, LTE6217, and LTE6262 according to the long elimination half-life of the compound. It was measured on two sleep parameters reported by the patients on the daily sleep questionnaire and calculated as a mean after 1 week and 2 weeks of treatment discontinuation and compared with baseline values.

The results of the analyses showed no worsening compared with baseline values (ie, no rebound phenomenon) for pr-WASO and pr-TST in both treatment groups after 1 week and 2 weeks of treatment discontinuation, in any Phase 2-3 studies.

Dependence or abuse potential

Eplivanserin abuse liability

The abuse potential of eplivanserin was clinically evaluated with specific analyses of TEAE clusters potentially related to drug abuse liability and reported in all completed Phase 1, 2 and 3 studies conducted with eplivanserin whatever the dose. A specific pharmacodynamic study was also performed in recreational drug users and compared the effects of eplivanserin 5 mg and 15 mg with placebo, using diazepam as a positive control (Study PDY10249).

No specific pattern of AE suggestive of abuse potential was observed with a significant higher incidence in eplivanserin groups compared with placebo. In addition, the human abuse potential study results indicated that the therapeutic 5 mg dose of eplivanserin had no perceivable subjective effects, while the 15 mg dose had minimal subjective effects on a few measures, but was significantly less than diazepam. These clinical results are consistent with the mechanism of action of 5-HT2 antagonism, and results from animal studies; eplivanserin showed no dissociative or hallucinogenic effects in Phase 2-3 clinical trials or in the human abuse potential study.

Eplivanserin dependence potential

The potential for withdrawal effect after treatment discontinuation was assessed using the Physician Withdrawal Checklist (PWC) at the end of treatment and at the end of the first week and second week of the run-out period in Phase 3 studies (Studies EFC6220, LTE6217, and LTE6262) but also by assessing the TEAEs spontaneously reported during the run-out periods.

The analysis of withdrawal symptoms after treatment discontinuation showed that overall, in clinical Phase 3 studies, the mean change from baseline of the PWC total score observed in the eplivanserin group was very small and would correspond to an average of 1 withdrawal symptom of mild intensity (each item/symptom of the PWC being scored from 0: not present to 3: severe).

For most of the patients (70 % to more than 90% depending on the symptom), the status of the symptoms reported in the PWC did not change between last visit under treatment and 1st and 2nd week of discontinuation. When some symptoms were reported as "worsened" in some patients, they included commonly in the 3 studies, anxiety/nervousness, irritability, dysphoric mood/depression, insomnia, fatigue, restlessness, diaphoresis, and headache. The most frequently reported symptom was insomnia.

Analyses of withdrawal symptoms based on spontaneous reporting of TEAEs during the run-out period of Phase 2-3 studies showed that very few adverse events (mainly anxiety, headache and nausea) that might be related to a withdrawal effect were spontaneously reported after abrupt discontinuation of eplivanserin 5 mg administered up to 12 months in insomniac patients.

Overdose

Reports of overdosage of eplivanserin in trials with insomniac patients are limited. In a repeated-dose tolerability study in a limited number of healthy subjects the most frequently reported adverse events with

doses of eplivanserin from 10 mg up to 80 mg/day for up to 7 days were dizziness, postural dizziness, headache and nausea. No major safety concern was observed.

In the event of overdose, treatment should be supportive and directed toward alleviating symptoms. There is no specific antidote available for eplivanserin or its metabolites. It is not known whether eplivanserin and/or its metabolites can be removed by dialysis.

Pregnancy

Limited data regarding eplivanserin administration during pregnancy are available since pregnant women and women of childbearing potential without effective contraceptive method were to be excluded from clinical studies with eplivanserin.

However, 5 cases of pregnancy were reported during the completed clinical studies in patients receiving eplivanserin 2 mg (1 case), 5 mg (2 cases) or placebo (2 cases). In the eplivanserin groups the outcomes were: normal delivery of a healthy baby (eplivanserin 2 mg) and one spontaneous abortion (eplivanserin 5 mg). One patient was lost to follow-up.

Additionally, in on-going clinical studies, 2 cases of pregnancy were reported in the eplivanserin group: one had spontaneous abortion and the second was still on-going at the submission time.

Risk Management plan

The overall objective of the proposed RMP is to ensure the safe and effective use of eplivanserin in the appropriate patient populations.

This RMP has been written according to ICH E2E Pharmacovigilance Planning Guideline, and is organized following the format of the "Template for EU Risk Management Plan", Annex C to the EMEA "Guideline on Risk Management Systems for Medicinal Products for Human Use" (EMEA/CHMP/96268/2005), into effect since 27-Sep-2006 (EMEA/192632/2006). The present document summarizes:

   the safety specifications of eplivanserin at the time of the present submission (data lock point 12 March 2008, with an additional review of serious adverse events (SAEs), adverse events of special interest (AESIs), and deaths in ongoing trials at the time of this primary cut-off date up to 19 June 2008), including the description of important identified and potential risks, and an epidemiological description of the expected target population (Section 1),

   the pharmacovigilance measures planned to further evaluate the risks (Section 2), and

   the activities proposed to mitigate those risks and preserve the benefits of eplivanserin in
the post-marketing conditions of use (Sections 3 and 4).

5 SUMMARY OF THE RISK MANAGEMENT PLAN

Table 38 – Summary of the RMP

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
Important identified risk		
Diverticulitis	Routine pharmacovigilance, special attention in PSURs Follow-up on cases with diverticulitis spontaneously reported, using specific forms *Epidemiological studies of background diverticulitis rate in the general and insomnia populations and risk factors for diverticulitis* (using THIN database in the UK and LabRx database in the US) Post-marketing safety outcome retrospective cohort study for eplivanserin (using THIN database in the UK and LabRx database in the US) Mechanistic study to evaluate the effect of eplivanserin on gastrointestinal transit time *in healthy subjects* *In vitro pharmacology study to evaluate potential effects of eplivanserin on colon motility or contraction in animals* *LCM clinical trials (including a study on long-term treatment of chronic insomnia (LTE11331))* *Post-Authorization Safety Study (PASS) (Non-interventional cohort of patients treated with eplivanserin in real-life practice in Europe)*	SmPC: contraindication of the use of eplivanserin in patients with a history of diverticulitis, recommendation to caution patients with diverticulosis about the increased risk of diverticulitis associated with eplivanserin use, and monitoring recommendations in case of patients experiencing abdominal pain (usually in the left lower quadrant) associated with altered gastrointestinal motility (such as constipation or diarrhea) or fever *Communication process on appropriate usage of eplivanserin* ▪ Prescriber information using several tools: direct mailing letter (Introductory Letter for HealthCare Professionals) and physician's guide to prescribing ▪ Patient information using several tools: patient information leaflet and patient information brochure
Important potential risks		
Consequences of orthostatic decrease in blood pressure in the elderly population	Routine pharmacovigilance, special attention in PSURs LCM clinical trials *(including a study on long-term treatment of chronic insomnia (LTE11331))* *Post-Authorization Safety Study (PASS) (Non-interventional cohort of patients treated with eplivanserin in real-life practice in Europe)*	SmPC: recommendation to monitor blood pressure (in both supine and standing positions) regularly in patients over 65 years using eplivanserin and to inform patients about the possibility of a sudden drop in their blood pressure when they are changing their position from lying down to standing

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
Potential for dependence (including withdrawal symptoms)	*Routine pharmacovigilance, special attention in PSURs* *LCM clinical trials (including a study on long-term treatment of chronic insomnia (LTE11331))* *Post-Authorization Safety Study (PASS) (Non-interventional cohort of patients treated with eplivanserin in real-life practice in Europe)*	*SmPC: Information that no clinically meaningful withdrawal symptoms were recorded during the 2 weeks following discontinuation of eplivanserin in the clinical trials*
Potential for abuse	*Routine pharmacovigilance, special attention in PSURs*	*This potential risk, kept under surveillance, has not been confirmed, and no information is deemed necessary in the SmPC*
Important missing information		
Experience in pregnancy	Routine pharmacovigilance, special attention in PSURs Use of a specific report form for spontaneous reports of pregnancies to better document the reported cases	SmPC: use of eplivanserin not recommended during pregnancy
Use in patients receiving analgesics (opioids and antimigraine preparations), psycholeptics (hypnotics and sedatives, anxiolytics and antipsychotics) and psychoanaleptics drugs (antidepressants and psychostimulants)	*Routine pharmacovigilance* *Post-marketing safety outcome retrospective cohort study for eplivanserin (using THIN database in the UK and LabRx database in the US)* *Post-Authorization Safety Study (PASS) (Non-interventional cohort of patients treated with eplivanserin in real-life practice in Europe)*	*SmPC: recommendation to caution patients about possible combined effects with CNS-active medicinal products when used concomitantly with eplivanserin*
Experience in lactating women (excretion in milk)	Routine pharmacovigilance, special attention in PSURs	SmPC: use of eplivanserin not recommended during breast feeding
Experience in children and adolescents (possible off label use)	Routine pharmacovigilance, special attention in PSURs	SmPC: use of eplivanserin not recommended in children and adolescents below 18 years
Experience beyond one year of exposure	Routine pharmacovigilance, special attention in PSURs	SmPC: information on clinical studies duration displayed
Experience in patients with severe hepatic impairment	Routine pharmacovigilance	SmPC: use of eplivanserin not recommended in patients with severe hepatic impairment

PHARMACOVIGILANCE PLAN

Sanofi-aventis will continue to monitor the safety profile of eplivanserin once the product is launched by:
    Routine pharmacovigilance practices allowing a comprehensive and global overview of post-launch safety profile;
    Follow-up on cases with diverticulitis and pregnancies spontaneously reported using specific forms;

Re-assurance of safety and efficacy, including increased benefit, in ongoing life-cycle management (LCM) clinical trials.

As the important identified risk of diverticulitis requires further assessment in order to better characterize this risk in real-life settings, epidemiological studies will also be performed in addition to the routine pharmacovigilance activities with the following objectives: (1) to estimate the background rate of diverticulitis in the insomnia population, and (2) to assess the postmarketing rate of diverticulitis in patients treated with eplivanserin, patients profiles and outcomes *vs.* those treated with hypnotic drugs. A mechanistic study is also planned to evaluate if eplivanserin has an effect on gastrointestinal transit time. This effect could contribute to the occurrence of diverticulitis in at-risk patients, and, if transit time is increased, this may be corrected by simple clinical measures to be determined.

SUMMARY OF SAFETY CONCERNS AND PLANNED PHARMACOVIGILANCE ACTIONS

Table 27 below summarizes all the planned actions to further assess and characterize the important identified and potential risks, as well as missing information.

Table 27 – Planned pharmacovigilance action(s)

Safety concern	Planned action(s)
Important identified risks	
Diverticulitis	Routine pharmacovigilance, special attention in PSURs
	Follow-up on cases with diverticulitis spontaneously reported, using a specific form
	Epidemiological studies of background diverticulitis rate in the general and insomnia populations and risk factors for diverticulitis (using THIN database in the UK and LabRx database in the US) *(Done. Study reports available in [Annexes 16, 17, 18 and 19])*
	Post-marketing safety outcome retrospective cohort study for eplivanserin (using THIN database in the UK and LabRx database in the US)
	Mechanistic study to evaluate the effect of eplivanserin on gastrointestinal transit time *in healthy subjects (Done. Study report available in [Annex 20])*
	In vitro pharmacology study to evaluate potential effects of eplivanserin on colon motility or contraction in animals
	LCM clinical trials (including a study on long-term treatment of chronic insomnia (LTE11331))
	Post-Authorization Safety Study (PASS) (Non-interventional cohort of patients treated with eplivanserin in real-life practice in Europe)

Safety concern	Planned action(s)
Important potential risks	
Consequences of orthostatic decrease in blood pressure in the elderly population	Routine pharmacovigilance, special attention in PSURs
	LCM clinical trials (including a study on long-term treatment of chronic insomnia (LTE11331))
	Post-Authorization Safety Study (PASS) (Non-interventional cohort of patients treated with eplivanserin in real-life practice in Europe)
Potential for dependence (including withdrawal symptoms)	*Routine pharmacovigilance, special attention in PSURs*
	LCM clinical trials (including a study on long-term treatment of chronic insomnia (LTE11331))
	Post-Authorization Safety Study (PASS) (Non-interventional cohort of patients treated with eplivanserin in real-life practice in Europe)
Potential for abuse	*Routine pharmacovigilance, special attention in PSURs*
Important missing information	
Experience in pregnancy	Routine pharmacovigilance, special attention in PSURs
	Use of a specific report form for spontaneous reports of pregnancies to better document the reported cases
Use in patients receiving analgesics (opioids and antimigraine preparations), psycholeptics (hypnotics and sedatives, anxiolytics and antipsychotics) and psychoanaleptics drugs (antidepressants and psychostimulants)	*Routine pharmacovigilance*
	Post-marketing safety outcome retrospective cohort study for eplivanserin (using THIN database in the UK and LabRx database in the US)
	Post-Authorization Safety Study (PASS) (Non-interventional cohort of patients treated with eplivanserin in real-life practice in Europe)
Experience in lactating women (excretion in milk)	Routine pharmacovigilance, special attention in PSURs
Experience beyond one year of exposure	Routine pharmacovigilance, special attention in PSURs
Experience in children and adolescents (potential off-label use)	Routine pharmacovigilance, special attention in PSURs
Experience in patients with severe hepatic impairment	Routine pharmacovigilance

Safety concern	Diverticulitis
Action proposed 2	**Epidemiological study of the background rate of diverticulitis in the insomnia population (using THIN database in the UK and LabRx database in the US)**
Objective of proposed action(s)	To allow an estimate of the background rate of diverticulitis in the population of patients with insomnia, to which the rate of the event in eplivanserin users can be compared
Rationale for proposed action(s)	Need to establish historical reference rate of diverticulitis in non-eplivanserin users insomnia patients due to limited available information in published data about background incidence/prevalence rates of diverticulitis in insomnia patients
	THIN is a UK observational database containing computerized information collected from 358 primary care practices throughout UK where all patients are registered with a general practitioner. Details of demographics, primary care diagnoses and prescription treatment are routinely recorded with the corresponding dates in individual patient records. Data on preventive medicine, details of referrals, secondary care diagnoses and deaths are also reported. The population included in THIN is representative of the UK population. Medical events are automatically coded at entry using a standard coding system. Because of its large size and its representation of the UK general population, THIN is suitable for epidemiological studies.
	LabRx® is collecting health information from a total of 35 million patients in the US, 21 million of whom are still enrolled in the United HealthCare Plan (current patients). If necessary, the patients can be contacted to collect more information.
Measures resulting of action results, decision criteria	Interpreting actual rates that will be estimated in post-marketing retrospective epidemiological studies in patients treated with eplivanserin
Milestones for evaluation and reporting including justification for choice of milestones	Results of background rates of diverticulitis in the insomnia population will be provided: ▪ for THIN database (UK GPs' medical record database) in Q4 09 ▪ for LabRx database (US Claim database (owned by United HealthCare) with possible link with medical records and US National Death Index) in Q2 09
Titles of protocols	The protocol of these epidemiological studies on diverticulitis in databases (THIN and LabRx) is provided in Annexes 7 and 8.
Action proposed 3	**Post-marketing safety outcome retrospective cohort study for eplivanserin (using THIN database in the UK and LabRx database in the US)**
Objective of proposed action(s)	To assess the post-marketing rate of diverticulitis in patients treated with eplivanserin, patients profiles and outcomes *vs.* those treated with hypnotic drugs; to provide the relative and excess risk of diverticulitis in eplivanserin users over comparison groups
Rationale for proposed action(s)	No information is available on the level of risk of diverticulitis due to eplivanserin use in real-life settings
Measures resulting of action results, decision criteria	Update of the SmPC information; and/or provide information via more urgent routes (dear HCP letter); and/or adjust the communication process on appropriate usage of eplivanserin, if the evaluation of risk of diverticulitis is modified compared to the one done based on clinical trials exposure, with subsequent integration in the risk minimization activities
Milestones for evaluation and reporting including justification for choice of milestones	Results will depend on the launch date in the UK and the US after marketing authorization approval, on the penetration rate, and on the capability of the selected databases to capture patients treated with eplivanserin. Relevant sample size is planned to be reached in the 2nd to 3rd year of commercialization.
Titles of protocols	The protocol of these post-marketing safety outcome studies on diverticulitis in databases (THIN and LabRx) is provided in Annexes 9 and 10.

The RMP is in general acceptable and is endorsed. There are however aspects that should be added or corrected as follows:

1) The concern of body weight changes persists. Even if no clinically significant abnormalities associated to the weight decrease have been observed during clinical trials, the impact of appetite disorders/body weight changes should be monitored in a larger population and in long-term treatment conditions, as expected with an insomnia treatment. Therefore, this concern should be followed-up as a potential risk in the RMP and should be included in the post-authorisation study.

2) The CHMP agrees that the consequences of the blood pressure decrease are the potential risk to be assessed, and not orthostatic hypotension, dizziness or vertigo by themselves. However, these events, which induce loss of balance, when linked to a decrease in blood pressure, may have some severe and serious consequences, mainly falls, and particularly in elderly patients. Therefore, the MAH should rename this potential risk into "Consequences of orthostatic decrease in blood pressure, dizziness and vertigo in the elderly population, including falls".

3) About the issue of infections it was concluded that what appeared to be an increase in infections in general was mostly driven by just one study and this was also due to a unbalanced follow-up in that study. Therefore overall it was accepted that there was no such overall increase of infections beyond the issue of diverticulitis already discussed. Thus it was accepted that infections are not considered independently in the RMP. However, the risk of infections, other than diverticulitis, should then be considered as an ongoing potential safety concern with eplivanserin and should be followed within the PASS study.

4) Overall, the methodology of the PASS study could be acceptable. As stated above, the MAA should include in this study the assessment of the potential risk for abuse, and the potential risk of "Infections". Moreover, the MAA should ensure that elderly (>65 years) and very elderly patients (>75 years) will be satisfactorily represented in the study population.
A full and detailed protocol of this PASS should be validated in the scope of a follow-up measure.

5) It is noted that patients aged over 65 years old are not suitably represented in LabRx database, since at that age patients become covered by the government Medicare system and no longer enter the LabRx database. As a retrospective cohort study is planned with this database, the MAA should discuss its limits, notably regarding the capacity to provide relevant information on the risk of diverticulitis in elderly or very elderly population.

IV.   ORPHAN MEDICINAL PRODUCTS

N/A

V.   BENEFIT RISK ASSESSMENT

V.1   Clinical context

V.2   Benefits

Eplivanserin is an oral product, intended for the treatment of chronic insomnia, relatively easy to produce without major manufacturing difficulties. There are no important non-clinical concerns. The PK characteristics are straightforward without important or difficult to manage interactions.
Eplivanserin belongs to a new mechanism of action type of products intended for the treatment of insomnia. It is a selective 5-HT2A receptor antagonist and is presented by the company as a new approach over sedative hypnotics to treat patients with primary insomnia towards modulating endogenous pathways that control the sleep-wake cycle and enhancing Slow Wave Sleep (SWS). The mechanism of action and the activity on enhancing SWS was supported by the combination of the brain PET imaging data, the effect

on 5-HT-induced platelet aggregation, and the effect observed on sleep architecture in polysomnographic recordings.

The clinical development program supporting the demonstration of the efficacy and safety of eplivanserin 5 mg/day in the intended indication "treatment of chronic insomnia with sleep maintenance difficulties as measured by duration and number of nocturnal awakenings" consisted of 5 randomized, double-blind, placebo-controlled, efficacy and safety studies in patients with primary insomnia as characterised by the DSM-IV-TR and sleep maintenance difficulties.

Efficacy studies were conducted in the sleep laboratory using polysomnography (PSG) and in an outpatient setting using daily patient questionnaires for short term - 4 (dose ranging subjective study) and 6 weeks (objective phase 3 study) - and long term duration - 12 weeks (2 pivotal subjective phase 3 studies). A 4 week comparative study to lormetazepam 1 mg/d was submitted later after the submission.

Both adult and elderly were included in the treated population and representing 1888 patients in the eplivanserin 5 mg group (including 322 elderly patients). The total sample size for efficacy evaluation in the targeted population was important and was considered satisfactory. However, in the phase III studies a total of 7087 patients were screened of whom 2964 patients were randomized. Less than half reached the double blind period, mainly due to stringent inclusion criteria related to disease characteristics. The large number of exclusion was due to the fact that the screened subjects did not meet the inclusion crieteria, ie, did not have maintenance insomnia of sufficient severity.

The 2 long term pivotal placebo controlled subjective studies (LTE6217 and 6262) in primary insomnia characterised by difficulties with sleep maintenance showed a modest effect on sleep maintenance as evidenced by a decrease of wake time after sleep onset (patient reported WASO) of 12 min as compared to placebo at 12 weeks. This positive effect was consistent with an increase in total sleep time and decrease of number of awakenings (TST of 14 min increase and NAW of -0.34 decrease as compared to placebo). Furthermore, the effect of eplivanserin on pr-WASO was shown in exploratory analyses to start on the first day of the treatment. Finally, eplivanserin showed a positive effect on sleep PSG sleep architecture analysis over placebo group on the time spent in stages 1 (lightest sleep decreased) and the time spent in stage 3-4 (increased deep sleep or slow wave sleep) with no effect on REM sleep duration.

The additional data was provided on responder analysis using several definitions and different imputation methods. In the pool of the 2 long-term studies, the difference of responder rates between placebo and eplivanserin corresponding to an improvement of at least 50% in the primary endpoint pr-WASO on observed cases (OC) at Week 12 was of 13% (and similar at Week 6). When the combined definition with improvement for the ability to concentrate is taken into consideration, the difference is about the same, 12% difference (with 49% in the eplivanserin group and 37% in the placebo group).

For the responder analysis with the WASO value at endpoint less or equal to 30 min alone, the difference of responder rates between placebo and eplivanserin in the pool of the long term studies is less important. At Week 12 it was of about 8% (10% at Week 6). When combined with improvement for the ability to concentrate, the difference is about the same (7.5% at week 12 and 9.9% at week 6).

The magnitude of the difference between both groups for these combined response rates based on observed cases is consistent whatever the hypothesis made on the missing data ie either all missing data imputed as non responder or analysis performed at the last available timepoint.

Two new studies which were ongoing at the time of the initial submission are presented with respective responder analyses:

- In the comparative study, there was almost no difference between eplivanserin and lormetazepam when the responder analysis included improvement of at least 50% pr-WASO as a parameter alone or combined with "no worsening" in the ability to concentrate. However, this was not the case when pr-WASO less or equal to 30 minutes was considered. A difference in favour of lormetazepam of 11% (criteria alone) and of 7% (combined with "no worsening" in the ability to concentrate) was observed.

-a 6-week randomised, double-blind placebo controlled polysomnography study where eplivanserin 5 mg/day was compared to placebo. Analysis of the co-primary efficacy endpoints showed that eplivanserin at week 6 improved sleep maintenance by decreasing PSG-NAW (LS mean change from baseline of -3.16, difference versus placebo -1.62, $p < 0.0001$). However, no difference was detected between the two groups on PSG-WASO at week 6.

Overall the new data allow the conclusion that eplivanserin 5mg/d is efficacious in the treatment of maintenance of sleep however there are still doubts about the clinical relevance of the effect size that is modest. Since the longest double-blind study has been 12 weeks in duration there is need to establish a maximum duration of treatment that can be considered supported by data.

Finally, up to now, residual and rebound effects, withdrawal symptoms and abuse seem not to be a concern with eplivanserin.

V.3   Risks

It is unclear whether the optimal dose has been found in the dose ranging study. Nevertheless it is considered that the data accrued for the 5 mg/d dose allows a judgment of its benefit-risk.

As regards safety, diverticulitis is a major identified risk with eplivanserin. Information on the physiopathology and mechanism that may explain this event with this type of drug is lacking. In addition, even if the analysis of cases of diverticulitis in clinical studies showed that the majority of patients had moderate non-complicated episodes of diverticulitis that resolved with antibiotic therapy, it remains that this risk emerged significantly compared to placebo. Diverticulitis can lead to life threatening complications (e.g stercoral peritonitis, abscess…), and may require treatments and surgery, as supported in clinical trials by the case of sigmoid abscess (recovered with antibiotic therapy), and the case requiring surgery for the management of recurrent episodes of diverticulitis.

There are some concerns regarding risks in elderly related to falls and orthostatic hypotension and during the concomitant use of other psychotropic medications that are not well characterized and that urged to be better studied in a PASS.

V.4   Balance

Currently the benefit of eplivanserin in the treatment of maintenance primary insomnia is still debated. The risk of diverticulitis is not yet sufficiently mitigated. We consider for the moment the benefit risk assessment unfavourable.

V.5   Conclusions

The overall B/R of eplivanserin is negative.