

**Public Assessment Report
for paediatric studies submitted in accordance
with Article 45 of Regulation (EC) No1901/2006, as
amended**

**(Zolpidem)
Stilnox**

UK/W/067/pdWS/001

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| Rapporteur: | UK |
| Finalisation procedure (day 120): | 25 March 2014 |
| Date of finalisation of PAR | 02 June 2014 |

TABLE OF CONTENTS

| | | |
|------|--|----|
| I. | Executive Summary..... | 4 |
| II. | RecommendationN | 5 |
| III. | INTRODUCTION | 6 |
| IV. | SCIENTIFIC DISCUSSION | 6 |
| IV.1 | Information on the pharmaceutical formulation used in the clinical study(ies)..... | 6 |
| IV.2 | Non-clinical aspects | 6 |
| IV.3 | Clinical aspects..... | 12 |
| IV.4 | Safety Review..... | 21 |
| V. | MEMBER STATES Overall Conclusion AND RECOMMENDATION | 34 |
| VI. | List of Medicinal products and marketing authorisation holders involved | 35 |

ADMINISTRATIVE INFORMATION

| | |
|--|---|
| Invented name of the medicinal product(s): | See section VI |
| INN (or common name) of the active substance(s): | Zolpidem |
| MAH (s): | See section VI |
| Pharmaco-therapeutic group (ATC Code): | Benzodiazepine related drugs N05CF02 |
| Pharmaceutical form(s) and strength(s): | 10mg film coated tablet |

I. EXECUTIVE SUMMARY

Summary of outcome

The current national SmPCs already contain relevant information, but a clarification in section 4.1 that the indication is for adults only and a more detailed description including details on study design, patient numbers and dose in section 5.1 are desirable.

As a result of this procedure, the text in accordance with the SmPC guideline 2009 has been agreed upon. The UK will maintain the current wording for section 4.3 'In the absence of data, zolpidem should not be prescribed for children' and consequently also the relevant cross-references in sections 4.2 and 5.1.

SmPC and PL changes are proposed in sections 4.1, 4.2 and 5.1

- No change
- New study data: <section(s) xxxx, xxxx>
- New safety information: <section(s) xxxx, xxxx>
- Paediatric information clarified: sections 4.1, 4.2, 5.1
- New indication: <section(s) xxxx, xxxx>

II. RECOMMENDATION

As a result of this procedure, the following text in accordance with the SmPC guideline 2009 has been agreed upon:

4.1 *Therapeutic indications*

Zolpidem is indicated for short-term treatment of insomnia in adults in situations where the insomnia is debilitating or is causing severe distress for the patient.

4.2 *Posology and method of administration*

Paediatric population

Zolpidem is not recommended for use in children and adolescents below 18 years of age, due to a lack of data to support use in this age group. The available evidence from placebo-controlled clinical trials is presented in section 5.1.

5.1 *Pharmacodynamic properties*

Paediatric population: Safety and efficacy of zolpidem have not been established in children aged less than 18 years. A randomized placebo-controlled study in 201 children aged 6-17 years with insomnia associated with Attention Deficit Hyperactivity Disorder (ADHD) failed to demonstrate efficacy of zolpidem 0.25 mg/kg/day (with a maximum of 10 mg/day) as compared to placebo. Psychiatric and nervous system disorders comprised the most frequent treatment emergent adverse events observed with zolpidem versus placebo and included dizziness (23.5% versus 1.5%), headache (12.5% versus 9.2%), and hallucinations (7.4% versus 0%) (see sections 4.2 and 4.3).

The UK will maintain the current wording for section 4.3 'In the absence of data, zolpidem should not be prescribed for children' and consequently also the relevant cross-references in sections 4.2 and 5.1.

A Type IB variation to be requested from the MAH within 60 days of this report

III. INTRODUCTION

One MAH submitted six completed paediatric studies for zolpidem in accordance with Article 45 of the Regulation (EC)No 1901/2006, as amended on medicinal products for paediatric use.

A short critical expert overview has also been provided.

Nonclinical data were provided from two company-sponsored juvenile rat studies and six published preclinical studies.

The MAH stated that the submitted paediatric studies do not influence the benefit risk for zolpidem and that there is no consequential regulatory action.

In addition, the following documentation has been included as per the procedural guidance:

- A line listing
- An annex including SmPC wording of sections 4.1 and 4.2 related to the paediatric use of the medicinal product.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the clinical study(ies)

Not provided.

IV.2 Non-clinical aspects

IV.2.1 Introduction

The MAH submitted reports for:

- One-month oral toxicity study of zolpidem administered to young rats ;
- Oral (gavage) study in juvenile rats;

The MAH submitted six publications relating to preclinical studies of zolpidem in juvenile animals.

IV.2.2 Non clinical studies

One-month oral toxicity study of zolpidem administered to young rats

➤ Methods

Zolpidem was administered orally by for a period of 30 to 31 days. Each treatment group consisted of 12 animals/sex with an equivalent control group receiving the vehicle.

- Species/strain/age: male and female Sprague-Dawley OFA rats, 7 days old at the start of the study
- Dose: 1, 2.5 and 10 mg/kg/day.

➤ **Results**

Sleep was the principal clinical sign observed, which occurred within the first 15 minutes after dosing and was dose related in duration, lasting between 15 and 75 minutes.

Bodyweight gain in the treated animals was comparable to control values, and the physical and behavioural development end points of the young rats were not affected by treatment. Hematological and clinical chemistry examinations did not reveal any modifications considered to be toxicologically relevant. Pathological examinations showed no effects on organ weights. Macroscopic and histopathological examinations did not reveal any treatment-related findings. Some renal changes (pelvic dilatation, hydronephrosis) were considered to be incidental, and the mild inflammatory changes with discrete proliferation of bile ducts was considered to be related to a mild concurrent infection. Other changes were considered to be incidental or due to gavage error or sacrifice method. Due to the young age of the animals at necropsy, the reproductive organs were immature. In conclusion, no toxic effects were observed when zolpidem was administered to young rats, and the no-observed-adverse-effect level (NOAEL) in this study was considered to be 10 mg/kg/day.

Oral (gavage) study in juvenile rats

The primary objective of this study was to evaluate the potential effects of long-term administration of zolpidem on growth, reproductive development, neurological and neurobehavioral development (overall CNS development, memory, cognition and brain morphology as well as reproductive function) .

➤ **Methods**

Zolpidem was administered orally daily by gavage once daily from PND 21- 62 to 4 groups of rats each consisting of 40 males and 40 females.

- Dose: 12.5, 25, 50 and 100 mg/kg/day daily by oral (gavage) administration for a period of 6 weeks from postnatal day (PND) 21, followed by a 7-week recovery period.
- Species/strain/age: male and female Crl:CD(SD) rats, postnatal day (PND) 21 at the start of the study

➤ **Results**

Mortality (12.5, 50 and 100 mg/kg/day group males and 50 and 100 mg/kg/day females), clinical findings (primarily neurobehavioral related to sedation, and not considered adverse, at all dosage levels for both sexes), lower mean body weight gains generally correlated with food consumption in the 12.5, 25, 50 and 100 mg/kg/day group males and lower mean body weight gains in the 25, 50 and 100 mg/kg/day group females were observed during the treatment period of this study. Delays in balanopreputial separation and vaginal patency were observed in the 50 and 100 mg/kg/day groups. Increased startle responsiveness (38% for VMAX and 28% for VAVE) was noted in the 100 mg/kg/day females on PND 60. These differences were not statistically significant compared to the control group values, and no effects were noted on PND

82 following the 20-day non-treatment period. There were no test article-related effects on locomotor activity or learning and memory during and following cessation of the treatment period and reproductive parameters, including survival of the embryos, following the cessation of dose administration at any dosage level. In the physiological domain, there were no changes other than lower mean body weights in the 12.5, 25, 50 and 100 mg/kg/day males and females. However, the other functional domains that evaluate neurobehavior including central nervous system (CNS) excitability, CNS activity, neuromuscular, autonomic and sensorimotor were unaffected. No test article-related macroscopic or microscopic findings (including brain morphology) or effects on organ weights were noted at any dosage level. Based on the results of this study, the NOAEL for general toxicity during childhood, adolescence and young adulthood was less than 12.5 mg/kg/day (AUC₀₋₂₄ of 1460 and 950 ng•h/mL SL80.0750 for males and females, respectively) based on mortality and body weight effects. The NOAEL for neurobehavioral toxicity was 50 mg/kg/day (AUC₀₋₂₄ of 2440 and 3490 ng•h/mL SL80.0750 for males and females, respectively) based on auditory startle response effects. The NOAEL for reproductive toxicity was the highest dosage level tested, 100 mg/kg/day (AUC₀₋₂₄ of 5050 and 8640 ng•h/mL SL80.0750 for males and females, respectively), as no effects on reproduction were observed.

➤ **Published preclinical studies related to juvenile animals**

A literature review was performed in Embase and Medline databases using the following strategy: ['zolpidem' /exp AND [animals]/lim] AND [juvenile odds ratio (OR) newborn OR neonate OR neonatal OR young OR immature OR prepuber* OR pup OR puppy OR kitten OR piglet OR infant OR fetus OR prenatal OR embryo OR postnatal NOT young:au] AND [adverse NEAR/1 effect OR adverse NEAR/1 reaction OR toxic* OR 'side effect' OR carcinogen* OR genotoxicity OR mutagen* OR teratogen* OR 'embryofetal development' OR 'developmental toxicity']

Six relevant publications were identified. They are mainly focused on potential interactions with brain receptors and brain development.

➤ **Seibt J, et al 2008. The non-benzodiazepine hypnotic zolpidem impairs sleep-dependent cortical plasticity. *Sleep*. 31(10):1381-91.**

The authors investigated the effects of 3 different classes of hypnotics on ocular dominance plasticity (ODP) in cats (male and female) in the critical period of visual development (postnatal days 28-41). After a baseline sleep/wake recording (6 h), cats received 6 h of monocular deprivation (MD) followed by an i.p. injection of triazolam (1-10 mg/kg i.p.), zolpidem (10 mg/kg i.p.), ramelteon (0.1-1 mg/kg i.p.), or vehicle (DMSO i.p.). They were then allowed to sleep ad lib for 8 h, after which they were prepared for optical imaging of intrinsic cortical signals and single-unit electrophysiology. Zolpidem reduced cortical plasticity by approximately 50% as assessed with optical imaging of intrinsic cortical signals. This was not due to abnormal sleep architecture because triazolam, which perturbed sleep architecture and sleep EEGs more profoundly than zolpidem, had no effect on plasticity. Ramelteon minimally altered sleep and had no effect on ODP. The authors conclude that alterations in sleep architecture do not necessarily lead to impairments in sleep function. Conversely, hypnotics that produce more "physiological" sleep based on polysomnography may impair critical brain processes, depending on their pharmacology.

- **Cannizzaro C, et al. 2002. Prenatal exposure to diazepam and alprazolam, but not to zolpidem, affects behavioural stress reactivity in handling-naïve and handling habituated adult male rat progeny. Brain Research. 953:170-80.**

Gentle long-lasting handling produces persistent neurochemical and behavioural changes and attenuates the impairment in the behavioural reactivity to novelty induced by the prenatal exposure to diazepam (DZ) in adult male rat progeny. This study investigated the consequences of a late prenatal treatment with three GABA/BDZ R agonists (DZ) alprazolam (ALP) and zolpidem (ZOLP)), on different stress-related behavioural patterns, in non-handled (NH), short-lasting handled (SLH) and long-lasting handled (LLH) adult male rats exposed to forced swim test (FST), acoustic startle reflex (ASR) and Vogel test (VT). The effects on motor activity were evaluated in the open field and in the Skinner box. The seizure sensitivity to picrotoxin (PTX) was investigated as an index of the functional state of GABA/BDZ Rs.

A single daily s.c. injection of DZ (1.25-2.50 mg/kg) and ALP (0.125-0.250 mg/kg) over gestational days 14-20 induced a decrease in immobility time in the FST in NH rats, no change in SLH rats and an increase in LLH rats; DZ induced an increase in the peak amplitude of the ASR in NH rats, no change in SLH rats and a reduction in LLH rats; ALP was ineffective in all groups. DZ and ALP reduced the number of punished licks in the VT in NH, SLH and LLH rats while the unpunished licks were not modified. DZ decreased locomotion and the lever pressing responses while ALP increased them. DZ and ALP increased the seizure sensitivity to PTX (2.5-4.0 mg/kg i.p.). These findings indicate a convergence on anxiety-related behaviours in the effects of prenatal exposure to DZ and ALP and a differentiation on motor activity. Long-lasting handling was able to overcompensate the increased behavioural stress reactivity induced by the prenatal exposure to DZ and ALP.

- **Cohen AS, Lin DD, Coulter DA. 2000. Transmission in Rat Hippocampal Area CA1 Neurons Protracted Postnatal Development of Inhibitory Synaptic. J Neurophysiol. 84:2465-76.**

The present study was designed to compare the allosteric coupling between the Cl⁻ channel of the GABA(A) receptor and the different benzodiazepine recognition site subtypes (BZ sites) in the cerebral cortex of newborn (5-day-old) and adult rats (90-day-old). To this aim, we reexamined the heterogeneity of cortical GABA(A) receptors in self- and cross-competition binding experiments using [3H]flunitrazepam and two ligands with higher affinity for benzodiazepine BZ2 sites relative to benzodiazepine BZ1 sites, the triazolopyridazine 3-methyl-6-[3-(trifluoromethyl)phenyl]-1,2,4-triazolo [4,3-b] pyridazine (CL 218,872) and the imidazopyridine N,N,6-trimethyl-2-(4-methylphenyl)-imidazo[1,2-a]-pyridine-3- hemitartrate (zolpidem). Benzodiazepine BZ1 sites accounted for 52% of the total number of binding sites in adult rats, but were not detected in newborn rats. On the other hand, two classes of benzodiazepine BZ2 sites with high and low affinity for zolpidem were present in newborn and adult rats. These sites were designated as benzodiazepine BZ2 (high affinity for zolpidem, K(d) ~ 150 nM) and benzodiazepine BZ(2L) (low affinity for zolpidem, K(d) ~ 3000 nM). High densities of benzodiazepine BZ(2H), sites were measured in both newborn and adult rats (75% and 41% of the total number of [3H]flunitrazepam binding sites, respectively), whereas benzodiazepine BZ(2L) sites accounted for 25% and 7% of the total number of cortical sites in neonates and adults, respectively. Flunitrazepam, CL 218,872 and zolpidem inhibited in a concentration-dependent manner the binding of [35S]t-butylbicyclophosphorothionate ([35S]TBPS) to the convulsant site of cortical GABA_A receptors in newborn and adult rats. The IC₅₀ for flunitrazepam was about 3 fold greater in adults than in neonates. This rightward shift in the concentration-response curve may be due to a decrease with age in the intrinsic efficacy of flunitrazepam. In contrast, CL 218,872 and zolpidem were 4-fold more potent at inhibiting [35S]TBPS binding in adult rats relative to neonates. The different affinities of CL 218,872 and zolpidem for benzodiazepine BZ1 and BZ2 receptors may account, at least in part, for the age-

related changes in their inhibitory potencies. These results demonstrate that benzodiazepine BZ2 sites mediate the modulation of [35S]TBPS binding by benzodiazepine recognition site ligands in the cerebral cortex of newborn rats. Further, benzodiazepine BZ2 sites may be involved in the inhibition of [35S]TBPS binding by flunitrazepam, CL 218,872 and zolpidem in the cerebral cortex of adult rats.

- **Giorgi O, et al 1995. Modulation of [35S]TBPS binding by ligands with preferential affinity for benzodiazepine BZ 1 sites in the cerebral cortex of newborn and adult rats. Eur J of Pharmacol. 290:37-47.**

The present study was designed to compare the allosteric coupling between the Cl⁻ channel of the GABA(A) receptor and the different benzodiazepine recognition site subtypes (BZ sites) in the cerebral cortex of newborn (5-day-old) and adult rats (90-day-old). To this aim, we reexamined the heterogeneity of cortical GABA(A) receptors in self- and cross-competition binding experiments using [3H]flunitrazepam and two ligands with higher affinity for benzodiazepine BZ2 sites relative to benzodiazepine BZ1 sites, the triazolopyridazine 3-methyl-6-[3-(trifluoromethyl)phenyl]-1,2,4-triazolo [4,3-b] pyridazine (CL 218,872) and the imidazopyridine N,N,6-trimethyl-2-(4-methylphenyl)-imidazo[1,2-a]-pyridine-3- hemitartrate (zolpidem). Benzodiazepine BZ1 sites accounted for 52% of the total number of binding sites in adult rats, but were not detected in newborn rats. On the other hand, two classes of benzodiazepine BZ2 sites with high and low affinity for zolpidem were present in newborn and adult rats. These sites were designated as benzodiazepine BZ2 (high affinity for zolpidem, K(d) ~ 150 nM) and benzodiazepine BZ(2L) (low affinity for zolpidem, K(d) ~ 3000 nM). High densities of benzodiazepine BZ(2H) sites were measured in both newborn and adult rats (75% and 41% of the total number of [3H]flunitrazepam binding sites, respectively), whereas benzodiazepine BZ(2L) sites accounted for 25% and 7% of the total number of cortical sites in neonates and adults, respectively. Flunitrazepam, CL 218,872 and zolpidem inhibited in a concentration-dependent manner the binding of [35S]t-butylbicyclophosphorothionate ([35S]TBPS) to the convulsant site of cortical GABA_A receptors in newborn and adult rats. The IC₅₀ for flunitrazepam was about 3-fold greater in adults than in neonates. This rightward shift in the concentration-response curve may be due to a decrease with age in the intrinsic efficacy of flunitrazepam. In contrast, CL 218,872 and zolpidem were 4-fold more potent at inhibiting [35S]TBPS binding in adult rats relative to neonates. The different affinities of CL 218,872 and zolpidem for benzodiazepine BZ1 and BZ2 receptors may account, at least in part, for the age-related changes in their inhibitory potencies. These results demonstrate that benzodiazepine BZ2 sites mediate the modulation of [35S]TBPS binding by benzodiazepine recognition site ligands in the cerebral cortex of newborn rats. Further, benzodiazepine BZ2 sites may be involved in the inhibition of [35S]TBPS binding by flunitrazepam, CL 218,872 and zolpidem in the cerebral cortex of adult rats.

- **Rovira C, Ben-Ari Y. 1994. Benzodiazepines modulate calcium spikes in young and adult hippocampal cells. NeuroReport. 5:2125-9.**

GABA(A) receptor-independent effects of benzodiazepine receptor (BZ-R) agonists on calcium and barium spikes were recorded intracellularly in the presence of bicuculline from CA3 hippocampal cells of young and adult rats. Zolpidem (ω 1 BZ-R agonist), had no effects in young animals but decreased calcium and barium spikes and barium currents in adults. Midazolam (ω 1 and ω 2 BZ-R agonist) increased barium spikes in both young and adult animals. The effects on calcium spikes were more complex since a decrease was sometimes preceded by an increase. Thus, in adults zolpidem acting on ω 1 BZ-R reduced calcium influx while in young rats midazolam acting on ω 2 BZ-R increased barium influx. This modulation of calcium spikes by

benzodiazepines could be relevant because of the developmental role played by calcium dependent processes.

- **Rovira C, Ben-Ari Y. 1993. Developmental Study of Benzodiazepine Effects on Monosynaptic GABA-Mediated IPSPs of Rat Hippocampal Neurons. J Neurophysiol. 70(3):1076-85.**

The effects of type I (BZ1) and type II (BZ2) benzodiazepine receptor ligands on monosynaptic γ aminobutyric acid (GABA)(A)-mediated inhibitory postsynaptic potentials (IPSPs) and on responses to exogenously applied GABA were studied using intracellular recordings from CA3 pyramidal cells of rat hippocampal slices taken at different postnatal stages [postnatal day 4 (P4) P35]. 2. The effects of midazolam, a BZ1 and BZ2 receptor agonist, were tested on the monosynaptic IPSPs at different stages. Monosynaptic, bicuculline-sensitive IPSPs were evoked by hilar stimulation in presence of α -amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) and N-methyl- D-aspartate (NMDA) antagonists [6-cyano-7-nitroquinoxaline-2,3-dione (10 μ M) and D(-)-2-amino-5-phosphonopentanoic acid (50 μ M)]. Midazolam at 300 nM maximally increased the duration and amplitude of monosynaptic GABA(A)- mediated IPSPs in neurons from pups (P4-P6, n = 6) and young (P7-P12, n = 8) and adult (P25-P35, n = 9) rats. All the effects of midazolam on IPSPs were reversed by the antagonist Ro 15-1788 (10 μ M). 3. The effect of midazolam was also tested on the response to exogenously applied GABA (5 mM) in the presence of tetrodotoxine [TTX (1 μ M)]. In neurons from young rats (n = 9), midazolam (1 nM-1 μ M) did not change the responses to exogenously applied GABA, whereas in adult rats (n = 8) midazolam maximally increased GABA currents at 30 nM. 4. The effect of zolpidem, a BZ1 receptor agonist, was tested on monosynaptic IPSPs and GABA currents at different stages. Zolpidem (10 nM-1 μ M) was inactive in cells from young rats (n = 12). In neurons from adult rats, zolpidem maximally increased the duration and amplitude of the monosynaptic IPSPs at 300 nM (n = 5) and the amplitude of GABA current at 30- 100 nM (n = 5). 5. Methyl-6,7-dimethoxy-4-ethyl- β -carboline-3-carboxylate (DMCM) (300 nM), an inverse agonist of BZ1 and BZ2 receptors, decreased the amplitude and duration of monosynaptic IPSPs in neurons from pups (n = 3) and young (n = 4) and adult (n = 5) rats. In all cases, full recovery was obtained after exposure to Ro 15 1788 (10 μ M). DMCMF (300 nM-10 μ M) failed to reduce GABA responses in cells from young (n = 3) or adult (n = 7) rats. 6. Results indicate that the regulation by benzodiazepine of GABA(A)-mediated IPSPs varies with the developmental stage. In young animals (before P13- P15), benzodiazepine action is mediated via BZ2 receptors, whereas in adult animals BZ1 receptors are implicated. Mechanisms of benzodiazepine action are also different in young and adult animals. In the adult, BZ1 and BZ2 agonists seem to modify GABA(A)-mediated IPSPs by a postsynaptic modification of the GABA(A) receptor. In younger animals, possible mechanisms involved in the action of BZ2 receptors are discussed.

IV.2.3 Discussion on non-clinical aspects and conclusion

Given that available clinical data do not support the use of zolpidem in the paediatric population, it is considered that the presented non-clinical data do not merit reflection in the product information. The SmPC guideline requires inclusion only of information on any findings in the non-clinical testing which could be of relevance for the prescriber in recognising the safety profile of the medicinal product *used for the the authorized indication(s)*. There is no authorized paediatric indication for zolpidem, and the SmPC states clearly that 'Zolpidem is not recommended for use in children and adolescents below 18 years of age'.

IV.3 Clinical aspects

IV.3.1 Introduction

Four pharmacokinetic/pharmacodynamic (PK/PD) studies with zolpidem were reported in children from 2 to 18 years after single oral administration of zolpidem with doses ranging from 0.125 mg/kg to 0.6 mg/kg.

The Clinical Expert Overview discusses the following studies:

| Study Title | Design | Subjects | Reported outcome |
|---|---------------|---|--|
| Study A | OL | 6 children with delayed growth | Zolpidem was rapidly absorbed with a mean peak concentration observed 1.3 hour post dosing with a mean plasma concentration at peak time of 142 ng/mL. The elimination half-life ranged from 1.4 hour to 3.1 hours and with an estimated plasma clearance ranged between 0.64 to 1.18 L/h/kg, indicating that the drug is cleared at a rate which is 2-3 times higher than that observed in adults (Cl = 0.86+/-0.1 versus 0.26+/-0.03 in adults). |
| Study B (published by Blumer et al) | OL | 62 children 2 – 18 years | The effect of age group was significant for AUC (P<0.02), T1/2 (P<0.04), mean residence time (MRT) (P<0.01), Cl/F (P<0.01), and Vdss/F (P<0.02). No age effects were observed for Cmax or Tmax. No significant correlations of any of the pharmacokinetic parameters with a change from baseline of any of the pharmacodynamic parameters. Fourteen patients experienced 22 adverse events, one was severe and possibly related (abnormal eye movement). (Source: Blumer et al) |
| Efficacy, safety and tolerability of zolpidem in the treatment of children aged 6 to 17 years with ADHD-associated insomnia (Study C) | R, DB, PC | 201 children aged 6 to 17 years with ADHD-associated insomnia | No evidence for hypnotic efficacy of zolpidem 0.25 mg/kg/day (with a maximum of 10 mg/day), based on polysomnography and actigraphy recordings, after 4 weeks of treatment. |
| Study D: Etude du Zolpidem et du Diazépam en prémédication orale avant anesthésie générale chez l'enfant | R, controlled | 200 children 4-16 years | Efficacy of zolpidem comparable to that of diazepam Safety: more children on zolpidem falling asleep and/or showing anxiety or agitation as compared to diazepam. |
| Study E: A study of Zolpidem in oral premedication prior to general anesthesia in children | OL | 11 children, 4 to 13 years | Mean dose of 0.30 mg/kg or 8 mg/m ² appeared to offer interesting possibilities as an oral premedicant prior to general anesthesia in children. Its half-life seemed comparable to that observed in healthy adult volunteers. |
| Study F: Zolpidem as oral premedicant in children before follow-up esophago-gastro-duodenoscopy: an open pilot study of efficacy and pharmacokinetics | OL | 10 children, no further details provided. | Administered doses of zolpidem do not appear to possess the features of a good premedicant in children. Zolpidem tmax values ranged from 0.3 to 2.0 hours with Cmax values between 123 to 444 ng/mL. The apparent elimination half-lives ranged from 0.8 to 3.0 hours with 6 cases showing values of 1 hour less. The PK data confirm that in children zolpidem is absorbed and eliminated at a faster rate than in adults. |

R = randomised, DB = double blind, PC = placebo controlled, OL = open label

IV.3.2 Clinical studies

➤ PK/PD studies

Four pharmacokinetic/pharmacodynamic (PK/PD) studies with zolpidem were reported in Children from 2 to 18 years after single oral administration of zolpidem with dose ranging from 0.125 mg/kg to 0.6 mg/kg. These studies are described below:

➤ **Study E : A study of Zolpidem in oral premedication prior to general anesthesia in children**

Eleven children, 4 to 13 years old (9.13 +/- 1.12 years), weighting 12 to 52 kg (28.8 +/- 4.13 kg) received either a 5 mg or a 10 mg dose of zolpidem (0.31+/-0.09 mg/kg) as an oral premedicant 45 to 155 minutes to general anaesthesia, and blood levels were collected following this single dose administration.

Elimination half-lives in children ranged from 0.7 to 1.9 hours and are comparable to those seen in the healthy volunteers. Height hours after the administration, zolpidem concentrations were very low and were not quantifiable 24 hours post dosing. Similar PK outcomes in children were reported in the reference.

There were no manifestations of clinical AEs. A slight transient disorientation was observed in 2 patients at 30 minutes, which could be attributed to an insufficient effect of the 5 mg dose of zolpidem at this observation time. No laboratory abnormalities were observed in the blood tests performed the morning after administration of zolpidem as compared to the baseline examination. A slight elevation of transaminases was observed, comparable to that seen with the atropine-alimemazine combination, during another study in the same center; this increase was attributed to the muscular consequences of surgery.

Assessor's comment

The study report states that 'Given the small number of samples a PK analysis of the data could not be performed. However, for 6 patients it was possible to estimate the apparent half life. These values have only an indicative value and a more in-depth PK analysis would have to be performed to confirm them.' This statement is clearly less affirmative than the one given by the company in their Clinical Overview. Quoted reference 9 has not been provided (Bianchetti G, Dubruc C, Thiercelin JF, et al. Clinical pharmacokinetics of zolpidem in various physiological and pathological conditions. In: Sauvanet JP, Langer SZ, Morselli PL editor. Imidazopyridines in sleep disorders: A novel experimental and therapeutic approach. New York: Raven Press; 1988:155–163.).

➤ **Study F: Zolpidem as oral premedicant in children before follow-up esophago-gastro-duodenoscopy: an open pilot study of efficacy and pharmacokinetics**

The aim of this study was to evaluate the activity of a 0.5% zolpidem hemitartrate solution as oral premedicant in children before oesophago-gastro-duodenoscopy, and to establish the PK profile of this formulation in children.

Ten children were enrolled in the study and received a single oral dose of zolpidem starting from the lowest dose 0.2 mg/kg up to the 0.6 mg/kg as oral premedicant before endoscopy.

There were 7 females and 3 males with age ranging from 4 to 12 years and body weight ranging from 18.4 to 41.4 kg corresponding to a total dose ranging from 4.1 to 20 mg.

Zolpidem t_{max} values ranged from 0.3 to 2.0 hours with C_{max} values between 123 to 444 ng/mL. The apparent elimination half-lives ranged from 0.8 to 3.0 hours with 6 cases showing values of 1 hour less. (Sic!) The PK data confirm that in children zolpidem is absorbed and eliminated at a faster rate than in adults.

The Lindsay sedation scale was rated just before zolpidem administration, after 30 and 60 min and 30 minutes after the end of the procedure. Mean rates differed from baseline during the first hour after ingestion but not post-procedure. It was concluded that the administered doses of zolpidem do not appear to possess the features of a good premedicant in children.

Five patients were reported to have AEs after the administration of zolpidem, ie diplopia (n = 4), oneirism (n = 4) and vertigo (n = 1).

Rapporteur's comment

The authors state that only 10 of the planned 15 patients were enrolled and the administration schedule was not respected owing to the substantial lack of efficacy and to the difficulty in coping with the oniroid symptoms after administration. They conclude that zolpidem does not possess the features of a good premedicant in children.

The information does not merit reflection in the product information.

➤ **Study A: Nocturnal pharmacokinetics of zolpidem in children**

The nocturnal PK profile of zolpidem was evaluated in 6 children with delayed growth following a single oral administration of zolpidem. Children were 8 to 14 years old with a body weight ranging from 17.0 kg to 34 kg and receiving zolpidem dose of 0.29 to 0.58 mg/kg.

Zolpidem was rapidly absorbed with a mean peak concentration observed 1.3 hour post dosing with a mean plasma concentration at peak time of 142 ng/mL.

The elimination half-life ranged from 1.4 hour to 3.1 hours and with an estimated plasma clearance ranged between 0.64 to 1.18 L/h/kg, indicating that the drug is cleared at a rate which is 2-3 times higher than that observed in adults ($Cl = 0.86 \pm 0.1$ versus 0.26 ± 0.03 in adults).

Only one Adverse Event (AE) was reported: one hour after the 10-mg zolpidem dose ingestion, an 11-year-old child experienced a strange floating sensation, as if she was lying in a hammock. She also thought she had been moved to another room. These sensations were not unpleasant and only lasted 45 minutes. No corrective treatment was initiated and no change was made in the conduct of the kinetic study. This AE was considered to be certainly drug-related by the investigator.

Rapporteur's comment

The trial was double-blind placebo-controlled. Children were administered a single 10mg dose. There was 1 adverse event (floating sensation). The authors conclude that the results suggest that mg/kg doses 2-3 times higher than those used in adults should be used, if needed, in paediatric patients. The information does not merit reflection in the product information.

➤ **Study B: Single dose pharmacokinetic and pharmacodynamics evaluation of three different doses in children from 2 to 18 years of age**

Due to the limited number of studies on hypnotic use in children, the present study evaluated the PK and safety of three different doses of zolpidem following single dose administration in children aged 2–18 years with insomnia. This was a multicenter, open-label, dose-escalation study in children within three age groups (2–6, >6–12, >12–18 years) with insomnia. Zolpidem administered in liquid oral formulation to twenty-one subjects, seven from each age group, within each dose level [0.125 mg/kg, 0.25 mg/kg, or 0.50 mg/kg (20 mg max dose allowed)].

The PK outcomes demonstrated that zolpidem disposition in children is similar to that seen in adult patient. Peak plasma concentrations were reached in approximately one hour with the C_{max} demonstrating dose proportionality. The elimination half-life was dose independent at approximately 2.1 hours. Expected age-related differences in elimination half-life and AUC were noted but overall clearance and mean residence time were both age- and dose-independent.

PK/PD relationship taking into account the three primary PD sleep outcomes following (minutes of onset latency, minutes of true sleep time and percent efficiency showed that PK parameters do not predict sleep outcomes and the addition of PK parameters to multivariate models containing dose, age, baseline values, and their interaction of dose and age, does not change the conclusions drawn on models without them.

The report showed that based on these data a dose of 0.25 mg/kg up to a maximum dose of 20 mg should be considered for evaluation of the safety and efficacy of zolpidem in children with sleep disturbances.

The information above is in contradiction to the cited publication (Blumer JL et al. 2008; Potential pharmacokinetic basis for zolpidem dosing in children with sleep difficulties. Clin Pharmacol Ther 83(4):551-8). Blumer et al note that significant pharmacokinetic effects by age group included an increase in AUC (P¼0.02), half-life (P¼0.04), and mean residence time (P¼0.01), whereas total body clearance decreased (P¼0.01) and steady-state volume of distribution was variable. In the multiple regression models, no pharmacokinetic parameter was significant in any model for any sleep parameter. The authors conclude that their evaluation of zolpidem's effects on children diverges from the results of studies performed in adults in the linkage of pharmacokinetic and pharmacodynamic results. Pharmacokinetic measures have been shown to predict sleep outcomes in adults, but did not do so for patients in this study. In this study's population, zolpidem's effects on several sleep parameters exhibited a high degree of variability, potentially including paradoxical effects when the dose was either too high or too low for specific age cohorts. Although a detailed discussion of these sleep outcome results is beyond the scope of this paper, it is possible that pharmacologic age-related differences in receptor-binding affinity at the gamma aminobutyric acidA (GABAA) receptor, the concentration of GABAA receptors within the specific sleep-promotion brain region, as well as differences in the maturity of inhibitory neural circuitry may, in part, explain the variability in zolpidem-influenced sleep parameters between children and adults.

Rapporteur's comment

The authors note that this work was supported by the MAH.

Adverse events

The Table 1 shows the number of AEs when reported by at least 5 subjects and distributed by body system and age group. Psychiatric complaints, gastrointestinal disorders and nervous system disorders were reported across the age groups. No pattern of AEs was evident; most AEs were reported as "mild" and not related to study drug. Two AEs were reported as severe in the 2 - 6 year-old group. One subject (0.125 mg/kg dose group) reported a severe laceration of his hand and finger 11 days prior to receiving study drug. A second child in the same age group

(0.5 mg/kg dose group) reported "rapid, uncontrolled eye tracking" (abnormal eye movements) approximately 20 minutes after receiving drug. This AE was accompanied by tachycardia and hallucinations (both moderate in intensity). All these AEs resolved with no intervention.

Table 1 - Number of adverse events when reported by at least 5 subjects, distributed by body system and age group

| Body system | Age group (years) | | | Total |
|----------------------------|-------------------|---------|----------|-------|
| | 2 - 6 | >6 - 12 | >12 - 18 | |
| Infections | 4 | 3 | - | 7 |
| Psychiatric disorders | 3 | 1 | 2 | 6 |
| Gastrointestinal disorders | 2 | 1 | 3 | 6 |
| Nervous system disorders | 1 | 2 | 2 | 5 |

Table 2 shows possibly related Treatment Emergent AEs by preferred term, age and dose.

Table 2 - Possibly related treatment emergent adverse events (number of events) by preferred term, age group and dose

| Preferred term | Age group in years (dose in mg/kg) ^a | | |
|--------------------------------|---|-----------|-----------|
| | 2 - 6 | >6 - 12 | >12 - 18 |
| Tachycardia | 1 (0.5) | - | - |
| Abnormal Eye Movements/Rolling | 1 (0.5) | - | 1 (0.5) |
| Double Vision | - | - | 1 (0.5) |
| Anxiety | 1 (0.125) | 1 (0.25) | - |
| Disorientation/Confusion | 1 (0.5) | - | 1 (0.5) |
| Hallucination | 1 (0.5) | - | 2 (0.5) |
| Dizziness | - | 3 (0.25) | - |
| Diarrhea/Loose stool | 1 (0.5) | 1 (0.125) | 1 (0.125) |
| Elevated Bilirubin | - | - | 1 (0.125) |
| Dyspnoea | - | - | 1 (0.5) |
| Hiccups | 1 (0.5) | - | 1 (0.5) |
| Prothrombin time prolonged | - | 1 (0.25) | - |

^a Maximum dose ≤ 20 mg

Only one TEAE, "abnormal eye movements" was severe. All related TEAEs resolved with no intervention, except for the elevated bilirubin. This child in the > 12 - 18 year-old group received 0.125 mg/kg dose and demonstrated a mild elevation in bilirubin 12 hours after receiving study drug. Although the physician noted a positive relationship to study drug, this child had a history of sickle cell disease which was the likely explanation of the elevated bilirubin. No pattern of TEAE was evident.

No deaths occurred in this study.

One serious AE was reported in an 8-year-old subject who was in the middle dose range (0.25 mg/kg). More than 40 hours (20 half-lives) after receiving the drug, the child fell while playing and bruised his left hand. The child was seen in a local emergency room, the hand was splinted and the child was discharged. The investigator, while believing this to be a serious adverse event, recorded that it was unrelated to the drug.

Two subjects withdrew from the study because of an AE.

A 4-year-old male with a significant history of poor school performance and insomnia was enrolled in the study and tolerated all study-related procedures until the second sleep lab visit. After receiving zolpidem, he required almost four hours to fall asleep. Once asleep he rested comfortably for two hours and then awoke in an agitated state. At that point, his mother requested that the study be terminated with 2 blood samples remaining to be drawn. The patient was then discharged from the facility and was behaving normally on follow-up. At the time of discharge, the mother shared with the study team that the child had received a dose of 5 mg of zolpidem in the past and had manifested agitation to a similar degree. In the opinion of the investigator, this was an expected effect related to the dose of zolpidem being too low. According to the company, a paradoxical reaction to zolpidem may also be suspected in this case.

A 9-year-old female in the 0.25 mg/kg dose group withdrew from the study prior to acquiring any post-dose pharmacokinetic data. Approximately 15 minutes after dosing, the subject began to complain of dizziness. She became anxious and this escalated for the next hour. Her father and the sleep technician both tried to calm her without success. Her mother arrived and helped to console her but she requested to go home. She was released approximately 2 hours post dosing and was still wide awake. The mother noted in a follow-up visit that the child did fall asleep at home approximately 4 ³/₄ hours post dosing. Also noted during the follow-up phone call was another incidence of dizziness prior to going to sleep that occurred 9 days after the dose administration visit that was deemed possibly related to study drug by the investigator.

Clinical laboratory evaluations

Laboratory assessments were done at the screening and follow up visits. There was no pattern of abnormality reflected in the means of laboratory values within age or dose group, or in the change from baseline. Some changes that appeared meaningful were likely to be related to diet because subjects were not necessarily fasting at the time of blood draw.

Individual laboratory values

A 15-year-old male in the 0.125 mg/kg group demonstrated an elevated bilirubin (1.7 mg/dL) at follow up, a change outside the range of normal (0.2 - 1.2 mg/dL) and greater than his baseline value (1.2 mg/dL). His history of sickle cell disease was the likely explanation of this elevation in bilirubin.

Vital signs, physical finding, and other safety observations

There were no clinically meaningful changes in vital signs within age or dose group. There was no pattern of change in physical exam and no clinically meaningful changes over time.

Sub group analysis

Two subgroup analyses were performed: Attention Deficit Hyperactivity Disorder (ADHD) and Pervasive Developmental Disorder (PDD)

14/65 subjects had a diagnosis of ADHD. None of these children experienced serious AE. 2 children, one in the 2 – 6 year-old group and one in the 6 - 12 year-old group, both at the 0.25 mg/kg dose level, experienced an AE. The first event, pyrexia, was mild, considered not related

to study medication (started > 12 days before study drug administration), and resolved with no sequelae. The second event of prothrombin time prolonged was considered possibly related to the study drug and occurred 12 hours post dosing.

Vital signs for these children were generally within normal limits. Some children in all three age groups evidenced elevated heart rate at screening/baseline which carried over to the medication visit. However, there was no pattern of elevation associated with the medication visit for systolic or diastolic blood pressure, temperature, respiration or heart rate.

5/ 65 subjects had a diagnosis of PDD. None experienced serious AEs. One child in the 2 - 6 year-old group, at a dose of 0.125 mg/kg experienced a severe laceration, unrelated to study drug that resolved without sequelae. A child in the same dose group, but in the >6 - 12 year-old group experienced a sinus infection and elevated gamma-glutamyl-transferase prior to receiving study medication, and experienced right eye redness after the medication dose. All of these events were mild, required no intervention, and were not considered related to study medication. Vital signs for these children were generally within normal limits. Some children in all three age groups evidenced some elevated vital signs at screening baseline which carried over to the medication visit. However, there was no pattern of elevation associated with the medication visit for systolic or diastolic blood pressure, temperature, respiration or heart rate.

Rapporteur's comment

The provided safety data do not raise any new safety concerns.

➤ **MAH's conclusion on PK/PD studies**

In children and adolescent (2 years to 18 years), PK parameters reported in the different studies are consistent and the PK characteristics and outcomes demonstrated that zolpidem disposition in children were similar to that seen in adult patient. The compound was rapidly absorbed with peak plasma concentrations rapidly reached in approximately one hour after dosing, C_{max} demonstrating a dose proportionality. The compound is rapidly eliminated with values between 1h to 3 hours, and elimination half-life is independent of the dose. No PK/PD relationship were observed between PK and PD sleep outcomes parameters. No PK data are available in the paediatric population from birth to 2-year-old, in consequence no conclusion on the PK profile for this age category can be drawn.

➤ **Clinical Studies in Insomnia**

➤ **Efficacy, safety and tolerability of zolpidem in the treatment of children aged 6 to 17 years with ADHD-associated insomnia (Study C)**

The clinical trial was an international (USA and Canada) multicenter, stratified (ages 6 through 11, and 12 through 17 years) with imbalanced randomization (2:1), double-blind, placebo-controlled, and parallel groups study. A total of 201 patients were randomized in this study, with 111 patients exposed to zolpidem (up to a maximum of 0.25 mg/kg or 10 mg/day) for at least 8 weeks. The investigational product was zolpidem solution 2.5 mg/mL for orally administered 30 minutes before bedtime. Male or female children 6 through 17 years of age (up to the 18th birthday), with complaints of childhood insomnia, who have been diagnosed with ADHD (as defined by the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision [DSM-IV-TR] criteria) were included in the study.

Endpoints

The primary efficacy variable was latency to persistent sleep (LPS) measured by polysomnography (PSG) that was to be done between Weeks 3 and 4, and if not possible between Weeks 4 and 6.

The secondary efficacy variables included:

Clinical Global Impression (CGI)-child – global improvement of insomnia;

CGI-child – global severity of insomnia;

CGI-parent/legal guardian – global improvement and severity of insomnia;

PSG sleep parameters other than LPS: wake time after sleep onset (WASO), number of awakenings after sleep onset (NAASO), and total sleep time (TST);

Actigraphic measures of sleep characteristics: (LPS and TST);

ADHD Rating Scale-IV;

School tardiness/attendance reports;

Conners' Continuous Performance Test-II (CPT-II).

There was no evidence for hypnotic efficacy of zolpidem 0.25 mg/kg/day (with a maximum of 10 mg/day), based on polysomnography and actigraphy recordings, after 4 weeks of treatment, in children and adolescents 6 through 17 years of age with ADHD-associated insomnia and no impact of zolpidem treatment on behavioral and cognitive components of ADHD was observed. A total of 201 patients were randomized in this study, with a total of 111 patients exposed to zolpidem for at least 8 weeks.

The incidence of patients with at least 1 TEAE was greater in the zolpidem group (62.5%) when compared with the placebo group (47.7%). There were no deaths during the study. One patient (in the placebo group) experienced at least 1 serious adverse event (SAE) that was treatment-emergent. Nine (6.6%) patients in the zolpidem group discontinued treatment due to TEAEs versus 0 in the placebo group. Psychiatric and nervous system disorders comprised the most frequent (> 5%) treatment emergent adverse events (TEAE) observed with zolpidem versus placebo and included dizziness (23.5% vs. 1.5%), headache (12.5% vs. 9.2%), and hallucinations (7.4% versus 0). Nine (6.6%) patients in the zolpidem group discontinued treatment due to TEAEs versus 0 in the placebo group.

➤ **Clinical Studies in Other Indications**

➤ **Study D: Etude du Zolpidem et du Diazepam en prémédication orale avant anesthésie générale chez l'enfant**

Randomized, controlled double-blind study of zolpidem vs. diazepam as oral premedication before surgery in 200 children 4-16 years old weighing 12-60 kg. It found the efficacy of zolpidem to be comparable to that of diazepam, with more children falling asleep and/or showing anxiety or agitation prior to general anesthesia under zolpidem than under diazepam.

No significant difference was noted between zolpidem and diazepam for cardiac frequency, respiratory frequency, systolic blood pressure and diastolic blood pressure; 2 patients in zolpidem group and 1 patient in diazepam group experienced bradycardia. The mean score for nausea/vomiting was higher for zolpidem (0.11 ± 0.03) than for diazepam (0.01 ± 0.004); 12% children treated with zolpidem experienced nausea and/or vomiting. A dose-effect and differences between doses for zolpidem were evidenced for nausea/vomiting; there were no differences between doses for diazepam. Seventeen (17) patients in the zolpidem group and 7 patients in the diazepam group experienced vision disorders, mostly reported as diplopia, blurred vision or "colored vision of landscape". Other adverse effects included tracheal

hypersecretion (5 with both drugs), temporospatial disorientation (4 with zolpidem vs 0 with diazepam), erythematous rash (2 with zolpidem vs 1 with diazepam), bronchospasm (2 with zolpidem vs 4 with diazepam), agitation (1 with zolpidem vs 2 with diazepam).

➤ **Study E: A study of Zolpidem in oral premedication prior to general anesthesia in children**

11 children, 4 to 13 years old (9.13 ± 1.12 years), weighing 12 to 52 kg (28.8 ± 4.13 kg) received either a 5 mg (5 cases) or a 10 mg (6 cases) dose of zolpidem (0.31 ± 0.09 mg/kg) as an oral premedicant 45 to 155 minutes (89.0 ± 10.8 min) prior to general anesthesia. No other therapeutic sedative or vagolytic agent was administered. Efficacy was judged by the same evaluator from the state of consciousness and behavior prior to anesthesia and upon awakening, and was considered satisfactory in all cases.

In this preliminary open study, zolpidem, administered at a mean dose of 0.30 mg/kg or 8 mg/m² appeared to offer interesting possibilities as an oral premedicant prior to general anesthesia in children. Its half-life seems comparable to that observed in healthy adult volunteers.

A slight transient disorientation was observed in 2 patients at 30 minutes, which could be attributed to an insufficient effect of the 5 mg dose of zolpidem at this observation time. No laboratory abnormalities were observed in the blood tests performed the morning after administration of zolpidem as compared to the baseline examination. A slight elevation of transaminases was observed, comparable to that seen with the atropine-alimemazine combination, during another study in the same center; this increase was attributed to the muscular consequences of surgery.

➤ **MAH's Conclusion on Efficacy**

The available data on efficacy of zolpidem in insomnia in children and adolescents are limited to one study in a specific subgroup (ADHD-associated insomnia) and the results were negative. Therefore, they must be considered as insufficient to support a recommendation to use zolpidem for the treatment of insomnia in the paediatric population. Studies performed to evaluate zolpidem in anesthetic premedication are inconclusive and insufficient to support a recommendation to use zolpidem in this indication in the paediatric population.

IV.3.3 Discussion on clinical aspects and conclusion

The MAH's conclusion that PK characteristics and outcomes demonstrated that zolpidem disposition in children were similar to that seen in adult patient appears to be contradicted by the data cited by the MAH. The latter indicated significant pharmacokinetic effects by age. Given that a randomised controlled trial failed to demonstrate efficacy of zolpidem in children with ADHD-related insomnia, and given that information from this trial is already reflected in the SmPC, there is no requirement to reflect paediatric PK data in the product information.

The data for insomnia have already been assessed and there is therefore no need to assess them again. The findings are reflected in the current national SmPCs, but a more detailed description including details on study design, patient numbers and dose is desirable. As a result of this procedure, the following text has been agreed upon:

5.1 Pharmacodynamic properties

Paediatric population: Safety and efficacy of zolpidem have not been established in children aged less than 18 years. A randomized placebo-controlled study in 201 children aged 6-17 years with insomnia associated with Attention Deficit Hyperactivity Disorder (ADHD) failed to demonstrate efficacy of zolpidem 0.25 mg/kg/day (with a maximum of 10 mg/day) as compared to placebo. Psychiatric and nervous system disorders comprised the most frequent treatment emergent adverse events observed with zolpidem versus placebo and included dizziness (23.5% versus 1.5%), headache (12.5% versus 9.2%), and hallucinations (7.4% versus 0%) (see sections 4.2 and 4.3).

Zolpidem is not licensed for use as premedication in any age group. The provided paediatric data in this indication do not merit reflection in the product information.

IV.4 Safety Review

A search was performed in the MAH's global pharmacovigilance database to retrieve serious solicited related (either by the investigator or the company) and all medically-confirmed and non-medically-confirmed unsolicited cases, reported since zolpidem launch to 31 March 2013 in the paediatric population, i.e. patients aged less than 18 years, and exposed to zolpidem. Up to 31 March 2013, 375 unsolicited cases and 2 serious solicited cases involving patients aged less than 18 years treated with zolpidem were recorded in Sanofi global pharmacovigilance database.

Line listings and the CIOMS I reports for all cases and for all fatal cases were provided.

Serious solicited cases were as follows:

Serious related solicited cases

| Case | Id | Gender | Age | Events | Co-suspect drugs | Daily dose | Time to onset | Action taken | Outcome |
|--------------|----|--------|-----------|--|------------------|------------|---------------|--------------------------|---------------------|
| F01200602165 | | Female | 16 years | Poisoning, characterized by "light respiratory difficulty, anxiety sensation, ataxia, dyslalia, motor coordination difficulty, confusion, visual and auditory hallucinations and light oversight of recent memory" | - | 10 mg | 5 min | Permanently Discontinued | Recovered/ Resolved |
| F03200400037 | | Female | 24 months | Visual hallucination | - | - | 20 min | Unknown | Recovered/ Resolved |

The distribution of unsolicited cases in the different age-groups was the following:

- 6% (22/375) in infants aged \geq 28 days to < 24 months
- 23% (87/375) in children aged 24 months to < 12 years
- 71% (266/375) in adolescents aged \geq 12 to <18 years.

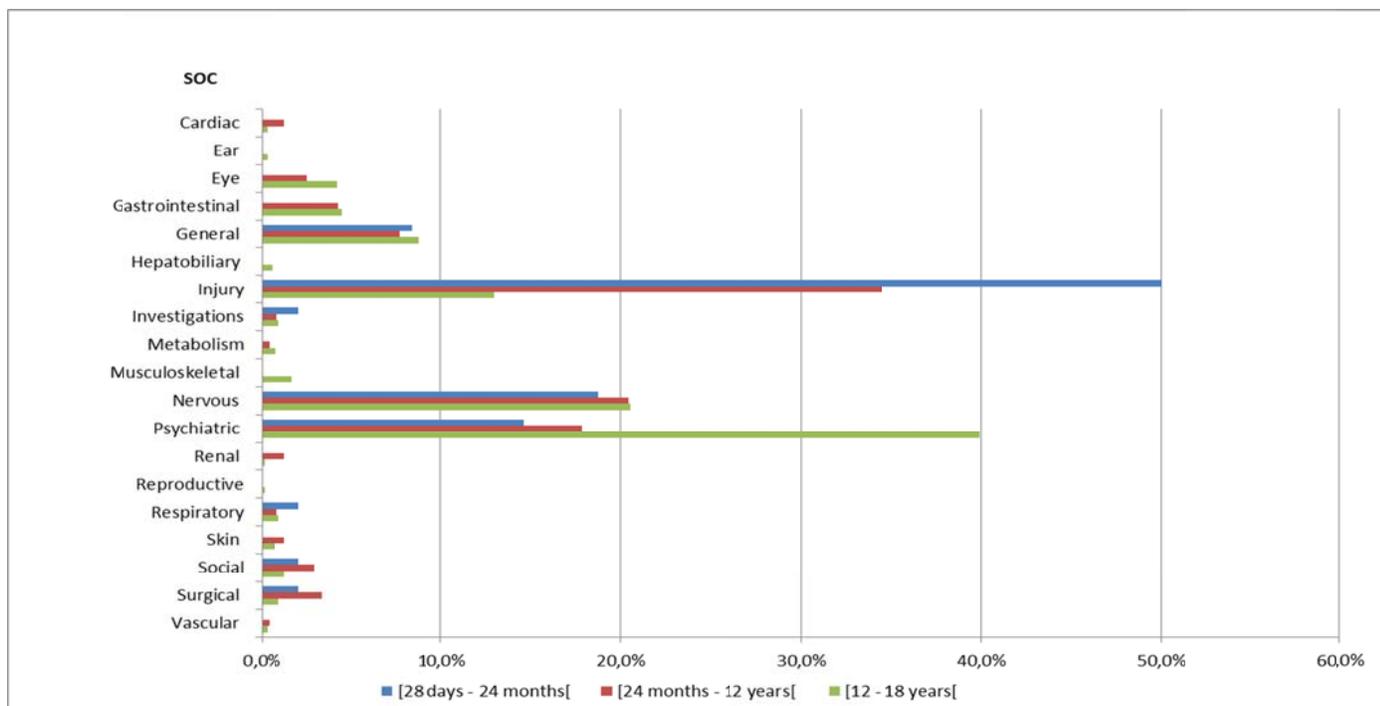
No cases were reported in neonates apart from a context of drug exposure during pregnancy and/or lactation. The majority of cases (n = 277) were medically confirmed. Among the 375

cases, 197 were serious and 178 non-serious. The proportion of serious cases was higher in adolescents (56%) than in infants (50%) or in children (41%).

The most commonly reported adverse reactions were overdose (139 cases), hallucinations (82 cases), somnolence (51 cases), agitation (34 cases), amnesia/amnesia anterograde (30 cases), dizziness/dizziness postural (26 cases), vomiting (25 cases), confusional state (23 cases) and accidental drug intake by the paediatric population (23 cases).

The distribution of the reactions by SOC among age-groups is presented in the Figure 1.

Figure 1 - Distribution of the reactions by SOC among age-groups



Details of most frequently involved Preferred Terms (PTs) in unsolicited cases among age-groups are provided in the table below.

Distribution and ratio of SOCs (in alphabetical order) with most frequently involved PTs in unsolicited cases among age-groups

| SOC | PT term | Age-group | | | Total |
|--------------------------------------|-----------------------|---------------------|----------------------|----------------|---------------|
| | | 28 days - 24 months | 24 months - 12 years | 12 - 18 years | |
| Eye disorders | Diplopia | - | - | 1.5% (11/711) | 1.1% (11/994) |
| | Mydriasis | - | 0.4% (1/235) | 1.0% (7/711) | 0.8% (8/994) |
| Total of cases | | - | 6.9% (6/87) | 10.2% (27/266) | 8.8% (33/375) |
| Gastrointestinal disorders | Nausea | - | 1.3% (3/235) | 1.4% (10/711) | 1.3% (13/994) |
| | Vomiting | - | 2.1% (5/235) | 2.8% (20/711) | 2.5% (25/994) |
| Total of cases | | - | 10.3% (9/87) | 10.5% (28/266) | 9.9% (37/375) |
| General disorders and administration | Drug ineffective site | - | - | 2.0% (14/711) | 1.4% (14/994) |

| SOC | PT term | Age-group | | | |
|--|------------------------------------|----------------------|-------------------------|-----------------|-----------------|
| | | 28 days 24 months | – 24 months 12 years | – 12 – 18 years | Total |
| conditions | Therapeutic response unexpected | - | 1.7% (4/235) | 1.1% (8/711) | 1.2% (12/994) |
| Total of cases | | 13.6% (3/22) | 18.4% (16/87) | 21.1% (56/266) | 20.0% (75/375) |
| Injury, poisoning and procedural complications | Accidental overdose | | | | |
| | Intentional overdose | | | | |
| | Multiple drug overdose | 29.2% (14/48) | 20.4% (48/235) | 10.8% (77/711) | 14.0% (139/994) |
| | Multiple drug overdose intentional | | | | |
| | Overdose | | | | |
| | Accidental drug intake by child | 12.5% (6/48) | 6.8% (16/235) | 0.1% (1/711) | 2.3% (23/994) |
| Total of cases | | 81.8% (18/22) | 71.3% (62/87) | 28.6% (76/266) | 41.6% (156/375) |
| Nervous system disorders | Amnesia | | | | |
| | Anterograde amnesia | - | 1.3% (3/235) | 3.8% (27/711) | 3.0% (30/994) |
| | Dizziness | | | | |
| | Dizziness postural | - | 3.0% (7/235) | 2.6% (19/711) | 2.6% (26/994) |
| | Somnolence | 10.4% (5/48) | 8.5% (20/235) | 3.7% (26/711) | 5.1% (51/994) |
| Total of cases | | 40.9% (9/22) | 42.5% (37/87) | 39.5% (105/266) | 40.3% (151/375) |
| Psychiatric disorders | Agitation | 4.2% (2/48) | 1.7% (4/235) | 3.9% (28/711) | 3.4% (34/994) |
| | Confusional state | - | 1.3% (3/235) | 2.8% (20/711) | 2.3% (23/994) |
| | Hallucination | | | | |
| | Hallucination, auditory | | | | |
| | Hallucinations, mixed | 2.1% (1/48) | 4.3% (10/235) | 10.0% (71/711) | 8.2% (82/994) |
| | Hallucination, visual | | | | |
| Total of cases | | 22.7% (5/22) | 29.9% (26/87) | 60.9% (162/266) | 51.5% (193/375) |
| Total of reactions | | 48 (4.8%) | 235 (23.6%) | 711 (71.6%) | 994 (100%) |
| Total of cases | | 22 (5.9%) | 87 (23.2%) | 266 (70.9%) | 375 (100%) |

125 cases of overdose (defined as daily dose > 0.25 mg/kg/day or > 10 mg/day) were reported, with 12 cases reporting a fatal outcome.

| Rapporteur's comment | | |
|---|----------------------------------|--|
| The following table provides an overview of deaths: | | |
| | Age, gender | Reactions |
| 1 | 14 year old girl | Completed suicide, homicidal ideation, akathisia, psychotic reaction, hallucinations. |
| 2 | 16 year old boy | Sleep walking resulting in death by drowning. |
| 3 | Girl 'in her late teens' | Death NOS (found dead, drug screen: zolpidem). |
| 4 | 5 year old boy | Victim of homicide, cause of death: multiple drug overdose. |
| 5 | 7 year old boy | Victim of homicide, cause of death: multiple drug overdose. |
| 6 | 15 year old boy | Completed suicide (death by hanging, prior to that hospitalization due to overdose of zolpidem). |
| 7 | 17 year old boy | Completed suicide, death by suffocation |
| 8 | 5 month old boy | Death following intentional drug misuse, zolpidem administered by day care provider. |
| 9 | 5 months old, gender unspecified | Death following intentional drug misuse. |
| 10 | 23 months old boy | Death, victim of homicide (zolpidem + methadone). |
| 11 | 36 month old boy | Death following intentional drug misuse. |
| 12 | 4 year old boy | Death following accidental acute overdose, possibly homicide. |
| <p>All of the reported cases are following off-label use; the majority is suicide, homicide and intentional misuse. The dose stated for the boy who died by drowning as a result of sleep walking is 10mg zolpidem. Somnabulsim is a listed adverse reaction. These cases do not necessitate amendment of the product information in our view.</p> <p>No new information that would merit reflection in the product information was identified.</p> | | |

The overall ratio of overdose cases was 33% (125/375); this ratio was higher in infants (59.1%) and children (51.7%) than in adolescents (33.3%).

The MAH states that the majority of the adverse reactions reported within the context of zolpidem overdose are in accordance with the safety profile of zolpidem in adult population, since most of them are listed with zolpidem, even at therapeutic dose.

The distribution of SOCs with most frequently involved PTs in overdose is presented in table 5

Table 3 - Distribution of SOCs with most frequently involved PTs in overdose unsolicited cases among age-groups

| Age-group | SOC | PT | Frequency |
|----------------------|--|------------------------------------|----------------|
| 28 days – 24 months | Injury, poisoning and procedural complications | Accidental overdose | 37.9% (11/29) |
| | | Intentional overdose | 3.4% (1/29) |
| | | Overdose | 6.9% (2/29) |
| | Nervous system disorders | Somnolence | 13.8% (4/29) |
| | Total of reactions | | 29 |
| Total of cases | | 13 | |
| 24 months – 12 years | Injury, poisoning and procedural complications | Accidental overdose | 19.0% (30/158) |
| | | Intentional overdose | 4.4% (7/158) |
| | | Multiple drug overdose | 1.9% (3/158) |
| | | Overdose | 5.1% (8/158) |
| | Nervous system disorders | Somnolence | 9.5% (15/158) |
| | | Ataxia | 3.2% (5/158) |
| | Psychiatric disorders | Hallucination | 4.4% (7/158) |
| | | Hallucination, visual | |
| | | Abnormal behaviour | 1.9% (3/158) |
| | | Agitation | 1.9% (3/158) |
| Total of reactions | | 158 | |
| Total of cases | | 45 | |
| 12 – 18 years | Injury, poisoning and procedural complications | Accidental overdose | 4.2% (8/192) |
| | | Intentional overdose | 25.5% (49/192) |
| | | Multiple drug overdose | 1.6% (3/192) |
| | | Multiple drug overdose intentional | 2.6% (5/192) |
| | | Overdose | 6.3% (12/192) |
| | Nervous system disorders | Somnolence | 8.9% (17/192) |
| | | Coma | 2.1% (4/192) |
| | Psychiatric disorders | Drug abuse | 3.6% (7/192) |
| | | Hallucination | 3.6% (7/192) |
| | | Hypnagogic hallucination | |
| | Agitation | 2.1% (4/192) | |
| Total of reactions | | 192 | |
| Total of cases | | 67 | |

The causes of death in the context of an overdose (n=12) are presented by age-group in Table 4. In 6 cases, an overdose was reported; in other cases, high levels of zolpidem were reported (n = 2) or zolpidem was detected in blood, urine and stomach contents (n = 1).

Table 4 - Causes of death among age-groups

| Age-group | Causes of death |
|----------------------|---|
| 28 days - 24 months | Respiratory arrest (n = 1), homicide by drug intoxication with methadone involving child's father (n = 1), unknown (n = 1) |
| 24 months - 12 years | Suspicion of homicide by zolpidem overdose involving child's mother (n = 1), homicide by multiple drugs overdose involving child's father or mother (n = 3) |
| 12 - 18 years | Drowning (n =1), freezing in forest (n = 1), suicide (n = 3) |

Literature review

A search on adverse reactions in paediatric population treated with zolpidem was performed in Medline and Embase databases.

The MAH identified 21 case reports which are included in above analysis.

- **Inagaki Adverse reactions to zolpidem: Case reports and a review of the literature. Prim Care Companion J Clin Psychiatry. 2010;12.**

Case 1 - sleepwalking due to drug interaction between zolpidem and fluvoxamine in a 15-year-old patient and case 2 - hallucination and sensory distortion in a 16-year-old patient).

Rapporteur's comment

Included in above analysis.

- **Echizenya M et al, Paradoxical reactions to hypnotic agents in adolescents with free-running disorder. Psychiatry Clin Neurosci. 2009 Jun;63(3):428.**

Case- paradoxical reactions, confusional state and agitation in a 14 year-old patient.

Rapporteur's comment

The case reported in this publication is as follows: 14-year-old boy suffered from an irregular sleep rhythm. He went to the general internal medicine clinic, and was prescribed zolpidem. After taking half of a 5-mg zolpidem tablet, he looked stern and was unable to stay still. He was confused and tried to run outside. He had little recollection of the experience. The authors conclude that the present report suggests that the use of hypnotic agents in adolescent patients with free-running disorder (non-24 hour sleep-wake syndrome) requires some consideration of the possible occurrence of paradoxical reactions.

- **Takayasu Distribution of zolpidem in body fluids and organ tissues in five autopsy cases. Forensic Toxicol. 2008;26(2):80-4.**

Case – adolescent found dead in forest, by freezing.

Rapporteur's comment

The publication does not provide any details for the one reported case of a 15 to 19 year old female who died of hypothermia and in whose tissues both zolpidem and amobarbital were detected.

- **Lange CL, Medication-associated somnambulism. J Am Acad Child Adolesc Psychiatry. 2005 Mar;44(3):211-2**

Case - somnambulism due to suspected interaction between zolpidem and venlafaxine in a 13-year-old patient with a history of multiple sleepwalking episodes when she was 8 and a strong family history of somnambulism.

Rapporteur's comment

The author notes that a Medline search for interactions found five cases of persistent hallucinatory activity when zolpidem was used with antidepressants, with venlafaxine noted among these (Elko et al., 1998). They also note that their case appears to be the first description of the induction of a somnambulistic episode as a result of combination of an SSRI with zolpidem. Although the mechanism of this is uncertain, because somnambulism is a disorder associated with slow wave sleep (SWS) and can be induced by standing a patient when in stage 3/4 sleep, one can hypothesize that this combination of medications could have created a rapid entry into SWS.

- **Andrade C, Zolpidem, vascular headache, and hallucinations in an adolescent. Aust N Z J Psychiatry. 2002 Jun;36(3):425-6.**

Case - hallucinations and delirium in a 13-year-old patient with a history of occasional rapid onset vascular headaches.

Rapporteur's comment

The authors suggest a possible interaction between zolpidem and vascular headache because vascular headache may itself be associated with hallucinatory phenomena, especially visual.

- **Elko CJ et al, Zolpidem-associated hallucinations and serotonin reuptake inhibition: A possible interaction. J Toxicol Clin Toxicol. 1998;36(3):195-203.**

Case - hallucinations in a 17-year-old patient concomitantly treated with bupropion, after intentional zolpidem acute overdose due to insomnia.

Rapporteur's comment

This publication includes on paediatric case of visual hallucinations lasting 3 – 4 hours in a patient who had been taking zolpidem 5 – 10mg daily for about 6 months and bupropion 450mg daily for a month without any adverse events. The hallucinations occurred when he intentionally increased his zolpidem dose to 60mg one night because of continuing insomnia. The authors discuss a possible pharmacodynamic interaction between serotonin and omega receptors that may be the basis of hallucinations when zolpidem is co-administered with an SSRI.

The UK SmPC contains the following information in section 4.5: 'Zolpidem tartrate appears to interact with sertraline. This interaction may cause increased drowsiness. Also, isolated cases of visual hallucinations were reported'.

➤ **Kurta DL et al, Zolpidem (Ambien): A pediatric case series. J Toxicol Clin Toxicol. 1997;35(5):453-7.**

Case 1 - accidental overdose with no reported reactions in a 20-month-old patient; Cases 2, 3, 4 - drowsiness after accidental overdose in a 19-month-old patient and two 5-year-old children ; Case 5 - drowsiness after intentional overdose in a 16-year-old patient ; Case 6 and 7- drowsiness and ataxia after accidental overdose in a 29-month-old child and a 4-year-old child ; Case 8 - drowsiness, ataxia and vomiting after intentional overdose in a 13-year-old patient ; Case 9 - drowsiness, dysarthria and sinus tachycardia after intentional overdose in a 14-year-old patient ; Case 10 - visual hallucinations after accidental overdose in a 4-year-old child ; Case 11 - hallucinations and agitation after intentional overdose in a 14 year-old patient ; Case 12 - nervousness after intentional overdose in a 12 year-old patient.

Rapporteur's comment

This is a retrospective case review of 12 children aged 20 months to 16 years, having ingested 2.5 to 150mg zolpidem. Symptoms, treatment and outcome are summarised in the table below. The authors concluded accidental paediatric ingestions of zolpidem were associated with minor CNS effects of short duration. Observation and supportive care appear to provide adequate intervention in these cases. When larger intentional or multiple drug ingestions are suspected, aggressive gastrointestinal decontamination may be warranted. They caution that their findings are limited by the small sample size as well as the lack of confirmation of the actual doses ingested and lack of laboratory analyses.

Table 1
Zolpidem Exposures

| Patient* | Age (y) | Amount (mg) | Onset of Symptoms (min) | Duration of Symptoms (h) | Coingestants | Symptoms | Diagnosis Site† | Treatment† | Outcome |
|----------|---------|-------------|-------------------------|--------------------------|--------------|-------------------------------------|-----------------|-------------|----------|
| 1 | 1.8 | 2.5 | 15 | | | None | ED | Observation | |
| 2 | 4 | 10 | 30 | 1 | | Hallucination | Home | Observation | Minor |
| 3 | 1.7 | 10 | 10 | 1 | | Drowsy | Home | Ipecac | Minor |
| 4 | 2.5 | 20 | 15 | 4 | | Drowsy, ataxic | ED | AC, IV | Minor |
| 5 | 4 | 10 | 30 | 2 | | Drowsy, ataxic | ED | AC | Minor |
| 6 | 5 | 30 | 60 | 4 | | Drowsy | ED | AC | Minor |
| 7 | 5 | 5 | 45 | Unknown | | Drowsy | Unknown | Unknown | Unknown |
| 8 | 12 | 12.5 | 60 | Unknown | | Nervous | Home | Observation | Minor |
| 9 | 15 | 20 | 60 | 6 | Prozac | Hallucination, agitation | ED | Observation | Moderate |
| 10 | 16 | 150 | 30 | 8 | Lasix | Drowsy | ED | LAV, AC, IV | Minor |
| 11 | 13 | 100 | Unknown | 10 | | Drowsy, ataxic, emesis | ED | AC | Minor |
| 12 | 14 | 100 | 60 | 6 | | Drowsy, slurred speech, tachycardia | ED | AC | Moderate |

*Patients 1-7 unintentional, patients 8-12 intentional. †ED, emergency department; AC, activated charcoal; LAV, lavage; IV, intravenous fluids.

- **Carbajal R et al, Flumazenil in zolpidem poisoning in children. Arch Pediatr. 1996 Feb;3(2):191-2.**

Case 1 - somnolence after accidental overdose in a 5-year-old child and Case 2 - somnolence after accidental overdose in a 3-year-old child).

Rapporteur's comment

The reference is a letter to the editor written in the French language. A translation has been provided. Both children were somnolent, were treated with flumazenil and recovered. The authors conclude that flumazenil can be used for children to counteract effects of a massive overdose of zolpidem.

An additional 8 relevant publications were identified from the literature and are discussed below. No safety concerns were identified by the MAH in these 8 publications.

- **Armour et al , 2008 A Randomized, Controlled Prospective Trial of Zolpidem and Haloperidol for Use as Sleeping Agents in Pediatric Burn Patients. J Burn Care Res 2008;29:238–247**

Children with burn injuries often require hospital treatment where they are subjected to stimuli likely to produce sleep deprivation. Previously demonstrated sleep fragmentation and significantly reduced sleep stage 3/4 and rapid eye movement in this population led to a search for sleep-enhancing interventions. The purpose of this study was to evaluate the effects of selected therapeutic interventions on sleep architecture. Forty patients with a mean (+/- standard error of mean) age of 9.4 +/- 0.7 years, mean total burn surface area of 50.1 +/- 2.9% and full thickness burns of 43.2 +/- 3.6% were randomly assigned to one of two treatment regimens using a blinded crossover design. Continuous polysomnographic recordings were obtained for six study periods. Each patient alternately received zolpidem one week and haloperidol the next, with the first monitored night conducted without medication. Zolpidem minimally increased the proportion of 3/4 and rapid eye movement sleep (0.81 +/- 0.16 vs 0.61 +/- 0.10 hrs, p = 0.02) but not total sleep time (4.8 +/- 0.3 vs 4.3 +/- 0.3 hrs on control nights, p = 0.1). Haloperidol significantly increased total sleep (5.3 +/- 0.3 vs 4.3 +/- 0.3 hrs on control nights, p = 0.02) and stage 2 sleep (3.3 +/- 0.3 vs 2.4 +/- 0.2 hrs, p = 0.001) compared with control nights. Both drugs slightly improved average sleep and wake period duration compared with control nights. Although sleep was somewhat improved by each test drug, there were no statistically significant differences between the drugs. Additional studies are needed to identify methods for improving restorative sleep postburn.

Rapporteur's comment

The authors conclude that in view of the results of this study, they no longer rely on zolpidem or haloperidol to improve sleep among acutely burned patients. The publication does not make reference to any adverse effects.

- **Gottschlich MM et al, 2009. An evaluation of the neuroendocrine response to sleep in paediatric burns patients. Journal of Parenteral and Enteral Nutrition 33,3 (317-326).**

Previous work demonstrated reduced stage 3+4 and rapid eye movement (REM) sleep following burn injury. This study evaluated the hormonal effects of drug intervention on measures of endocrine status. A secondary objective examined the relationship between hormones and sleep stage distribution. Forty patients 3-18 years of age with a mean percent total body surface area burn of 50.1 ± 2.9 were randomly assigned to zolpidem or haloperidol utilizing a blinded crossover design. Polysomnography was performed 6 nights, 3/ week over 2 weeks. Each

week's first night of monitoring was conducted without medication, serving as a baseline. Hormonal levels (epinephrine, norepinephrine, growth hormone, melatonin, dehydroepiandrosterone (DHEA), serotonin, cortisol) were obtained at 6 h each study day. Both drugs were associated with increased DHEA levels ($p < 0.03$); no other hormones were affected by medication. Significant inverse correlation was observed between REM sleep and epinephrine ($r = -0.34$, $p = 0.004$) and norepinephrine levels ($r = -0.45$, $p = 0.02$). A positive relationship existed between serotonin and sleep stage 3+4 ($r = 0.24$, $p = 0.01$) and REM ($r = 0.48$, $p = 0.01$). No other significant associations were identified between hormones and sleep. This work characterizes the relationship between sleep deprivation and select endocrine parameters postburn. Drug interventions utilized in this study were either ineffective or insufficient in modulating improved hormonal response. Significance of zolpidem's and haloperidol's effect on serum levels of DHEA is unclear. The inverse correlation of epinephrine with REM may suggest that hypermetabolism associated with burns is partly due to lack of REM sleep. Questions remain regarding the effects of sleep deprivation on metabolism and clinical outcome.

Rapporteur's comment

The publication does not make reference to any adverse effects.

➤ **Koirala et al, 2006 ; A comparative evaluation of newer sedatives in conscious sedation; J Clin Pediatr Dent 30(4):273-276, 2006**

This double blind study was undertaken to determine the safety and efficacy of orally administered newer sedatives and analgesics for conscious sedation in 120 child patients aged between 2 to 9 years. Patients were randomly assigned into: midazolam (I), ketamine (II), zolpidem (III), midazolam plus ketamine (IV), midazolam plus tramadol (V) and zolpidem plus tramadol (VI) groups of 20 each. Onset of action, level of sedation, ease of treatment completion, recovery time, and post-operative amnesia were assessed for all and compared. Midazolam plus ketamine was found the most effective combination providing a fast and adequate analgo-sedation in anxious and uncooperative child patients. There was no significant change in any of the vitals except in patients who received zolpidem either alone or in combination. In these 2 groups, mild increase in heart rate and blood pressure were observed during the early period of treatment. However, a close observation on all the patients had been kept throughout the post-drug administration period until complete recovery was attained. No complications arose in any patient due to these changes,

Rapporteur's comment

Poor amnesiac effect was reported for zolpidem in addition to mild increase in heart rate and blood pressure. A few children of zolpidem groups were found to be uninhibited and in a very jolly mood (singing and dancing) after the administration of zolpidem. The authors conclude that zolpidem did not prove to be a satisfactory conscious sedative agent.

➤ **Blumer JL et al, 2008. Potential Pharmacokinetic Basis for Zolpidem Dosing in Children With Sleep Difficulties; Clinical Pharmacology & Therapeutics 83, 4 (551-558).**

The pharmacokinetics of zolpidem was assessed in an open-label, dose-escalation study in children with insomnia. Twenty-one children, 7 per age group (2 - 6 years, 6 - 12 years, 12- 18 years), received a single dose of zolpidem at one of the three dose levels (0.125, 0.25, or 0.50 mg/kg [20 mg maximum dose]). Multiple PK measures were assessed at nine post-dose intervals and pharmacodynamics was assessed by polysomnography and actigraphy. Significant PK effects by dose were observed only as linear increases in maximum concentration (C_{max} , $p < 0.001$) and area under the plasma concentration-time curve (AUC $p < 0.001$). Significant PK

effects by age group included an increase in AUC ($p = 0.02$), half-life ($p = 0.04$), and mean residence time ($p = 0.01$), whereas total body clearance decreased ($p = 0.01$) and steady-state volume of distribution was variable. PD measures were independent of the PK estimates. Fourteen (14) patients experienced 22 adverse events. Most of these events were mild and not related to the study drug. No parasomnias were observed. One adverse event (abnormal eye movement), possibly related to treatment in the 0.5 mg/kg dose group, was considered to be severe by the investigator. All events were resolved without intervention, with the exception of one patient who did not receive study medication and was treated for mild otitis media and an infection resulting from recent dental work. No pattern of TEAE relative to zolpidem dosing was evident. Overall, zolpidem was well tolerated and a paediatric dose of 0.25 mg/kg is recommended for future efficacy studies.

Rapporteur's comment

The publication contains below table of adverse events.

Table 7 Adverse events by body system and age group*

| Body system | Age group | | | Total |
|----------------|-----------|--------------|--------------|-------|
| | 2-6 years | > 6-12 years | >12-18 years | |
| Infections | 4 | 3 | — | 7 |
| Psychiatric | 3 | 1 | 2 | 6 |
| GI disorders | 2 | 1 | 3 | 6 |
| Nervous system | 1 | 2 | 2 | 5 |

AE, adverse events; GI, gastrointestinal. *Only number of patients with ≥ 5 AEs reported.

The authors note that it is possible that pharmacologic age-related differences in receptor-binding affinity at the gamma aminobutyric acid A (GABAA) receptor, the concentration of GABAA receptors within the specific sleep-promotion brain region, as well as differences in the maturity of inhibitory neural circuitry may, in part, explain the variability in zolpidem-influenced sleep parameters between children and adults.

They also note that zolpidem was well tolerated by most patients. All three age cohorts tolerated all three zolpidem dosage levels without clinically significant difficulties. Adverse events were generally mild in intensity and resolved without intervention. Many of the reactions “possibly” related to treatment were consistent with the known side effects of sedatives in adults. No further details regarding the nature of the observed adverse events are given.

➤ **Forrester MB, 2009; Pattern of Pediatric Zolpidem Ingestions Reported to Texas Poison Control Centers, 2000 to 2006; *Pediatr Emer Care* 25: 26-30**

The purpose of this study was to describe the pattern of zolpidem ingestions by young children reported to poison control centers. Cases were all zolpidem ingestions by children 0 to 5 year old reported to Texas poison control centers during 2000 to 2006. Multiple substance ingestions were excluded. The distribution of the cases was described with respect to such demographic and clinical factors as patient gender, ingestion reason, ingestion site, management site, and medical outcome. There were a total of 463 cases, all unintentional exposures. The patient was male in 52.2% of the cases, and the exposure occurred at the patient's own home in 92.8% of the cases. The patient was managed on-site in 54.4% cases, already at or en route to a health care facility in 29.6% cases, and referred to a health care facility in 16.0% cases. Of the 322 cases with a known final medical outcome, 59.0% had no effect, 35.1% had minor effects, and 5.9% had moderate effects. The most frequently reported adverse clinical effects were drowsiness, ataxia, vomiting, and hallucinations. For most of the reported adverse clinical effects, the mean dose ingested in mg was greater than the 12.5 mg maximum formulation

available. In conclusion, paediatric ingestions of zolpidem alone reported to Texas poison control centers most frequently resulted in at most minor effects and were often managed at home.

Rapporteur's comment

The authors note the following limitations of their data: Reporting of zolpidem ingestions to Texas poison control centers is voluntary. Thus, it is unlikely that all such ingestions are reported to the TPCN. As a result, the data included in this investigation may be biased. In addition, there may be some questions as to the accuracy of the amount of zolpidem that a given child was reported to have ingested because the adults reporting the ingestions might not have actually witnessed the ingestion. It is even possible that no ingestion may have occurred at all. Another limitation is that all of the data variables were not available for every case. This is particularly true for reported dose and for final medical outcome. This may be an additional source of bias.

➤ **Ford JA et al, 2012 The misuse of Ambien among adolescents: Prevalence and correlates in a national sample. Addictive Behaviors 37, 1389–1394**

The current study examined data from the 2009 National Survey on Drug Use and Health, which includes a sample of more than 17 000 adolescents ages 12 to 17 years that is generalizable to the non-institutionalized population of the United States. The prevalence of lifetime Ambien misuse in the sample was 1.4%. Therefore, more than 300 000 adolescents in the United States are have misused Ambien at some point. The average age of the sample was 14.74 years old, 51% were male, 61% were white, and 56% reported a total family income of \$50 000 or more. Approximately 9% of the sample reported a major depressive episode in the past year, while about 21% reported tobacco use, 10% reported binge drinking, 15% reported marijuana use, 8% reported misuse of prescription drugs other than sedatives, and 7% reported the use of other illicit drugs.

In the bivariate logistic regression analysis where the impact of each independent variable was examined individually, older (Odds Ratio [OR] = 1.12) and white (OR = 1.54) adolescents were at an increased risk for Ambien misuse. Adolescents who were less religious (OR = 0.53), more delinquent (OR = 1.16), and those who reported a major depressive episode (OR = 4.16) were at increased risk for Ambien misuse. Providing support for Hirschi's social control theory, adolescents with strong bonds to parents (OR = 0.37) and school (OR = 0.71) were at a decreased risk for Ambien misuse. Consistent with Akers' social learning theory adolescents who reported that more of their peers used drugs (OR = 2.17) were more likely to report the misuse of Ambien. Also consistent with Akers' theory adolescents who held more conservative attitudes toward substance use (OR = 0.39), and also reported that their peers (OR = 0.41) and parents (OR = 0.39) held more conservative attitudes toward substance use were less likely to report Ambien misuse. Adolescents who experienced higher levels of strain (OR = 1.48) were also at an increased risk for Ambien misuse, consistent with Agnew's theory. Finally, respondents who reported tobacco use (OR = 4.47), binge drinking (OR = 5.25), marijuana use (OR = 7.28), other prescription drug misuse (OR = 14.17), and other illicit drug sue (OR = 8.80) were at an increased risk for Ambien misuse.

In the logistic regression model that included all independent variables together, younger respondents (Adjusted Odds Ratio [AOR] = 0.84) were at an increased risk compared to older respondents. Adolescents who came from homes with a total family income of greater than \$50 000 were at an increased risk for Ambien misuse (AOR = 1.63) than respondents from homes with a total family income of less than \$50 000. Both variables associated with Hirschi's social control theory were significantly associated with the misuse of Ambien, as respondents with stronger bonds to both parents (AOR = 0.70) and school (AOR = 0.61) were at a decreased risk for misuse. Finally, adolescents who reported marijuana use (AOR = 2.63) or other prescription drug misuse (AOR = 5.71) were at an increased risk for Ambien misuse compared to nonusers.

Rapporteur's comment

This publication provides data on the prevalence and correlates of zolpidem misuse in US adolescents: it does not include information that would merit reflection in the product information.

- **Bhatnagar S et al, 2012 ; Comparison of oral midazolam with oral tramadol, triclofos and zolpidem in the sedation of pediatric dental patients: An in vivo study. J Indian Soc Pedod Prev Dent [serial online] 2012 [cited 2013 May 30];30:109-14.**

The study was conducted out on 60 anxious and fearful children aged between 3-9 years who reported to the Department of Pedodontics and Preventive Dentistry in Rajasthan, India and were treated under conscious sedation for the accomplishment of dental treatment. Patients were randomly assigned to 4 groups: group I - midazolam 0.5 mg/kg body weight orally, group II tramadol 2 mg/kg body weight orally, group III- triclofos 70 mg/kg body weight orally and group IV- zolpidem 0.4 mg/kg body weight orally. There was a statistically significant difference in median scores recorded for the level of sedation between the different groups ($p < 0.001$). Midazolam was the best drug for producing conscious sedation followed by tramadol and triclofos. Zolpidem was not able to produce a sufficient level of sedation and it cannot be supported as a sedative agent at the present dosage.

Rapporteur's comment

In this study, drowsiness in some zolpidem patients was observed whereas some remained active throughout the stay in the clinic. Some of the patients after administration of zolpidem started speaking irrelevant things to their parents or to the operating dentist. Two patients were excluded from the study as they vomited the drug (zolpidem) out in 30 min time after administration.

- **Colle M et al, 1991; Nocturnal profile of growth hormone secretion during sleep induced by zolpidem: a double-blind study in young adults and children. Horm Res. 35(1):30-4.**

Overnight blood sampling for repeated growth hormone (GH) assays, regarded as the most physiological assessment of GH status, may induce some disturbances in patients' sleep and then in the evaluation of GH secretion. The influence of a hypnotic drug, zolpidem (10 mg), on nocturnal GH profiles (GH peak, time to first and maximum GH peak, area under the curve, mean integrated concentration) over two nights at a 7-day interval, was studied in a double-blind cross-over design in a group of 12 young adult volunteers (27.9 ± 4.3 years), and in a group of 12 children (10.8 ± 2.3 years) with short stature, in a parallel double-blind study. Mean GH profiles showed no difference between zolpidem-treated subjects and placebo-treated controls, either in adults or in children. Although in these experimental conditions, sleep onset latency was significantly reduced with zolpidem in the adult volunteers, the mean time to first GH peak remained unchanged. Furthermore, GH profile did not relate with sleep duration, sleep onset latency or number of awakenings. No AEs were recorded in the adult group. In the children group, only one AE was reported in this study: 1 h after the 10-mg dose ingestion, one child experienced a strange floating sensation, as if she was lying in a hammock. She also thought she had been moved to another room. These sensations were not unpleasant and lasted only 5 min. No corrective treatment was initiated and no change was made in the conduct of the kinetic study. The authors concluded that a hypnotic drug, such as zolpidem, given at bedtime, is therefore devoid of effect on nocturnal GH profile and may be used in young children for overnight blood sampling when needed.

Rapporteur's comment

This publication reports one non-serious adverse event in a child of unspecified age: it does not include information that would merit reflection in the product information.

IV.4.1 Discussion on safety aspects and conclusion

The safety review provided by the MAH does not raise any new safety concerns.

All of the reported cases of death are following off-label use; the majority is suicide, homicide and intentional misuse. The dose stated for the boy who died by drowning as a result of sleep walking is 10mg zolpidem. Somnabulsim is a listed adverse reaction. These cases do not necessitate amendment of the product information.

It is noted that the provided data do not allow for a comparison of any clinically relevant differences in adverse reactions between the adult and paediatric population.

V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION**➤ Overall conclusion**

The current national SmPCs already contain relevant information, but a clarification in section 4.1 that the indication is for adults only and a more detailed description including details on study design, patient numbers and dose in section 5.1 are desirable.

As a result of this procedure, the following text in accordance with the SmPC guideline 2009 has been agreed upon:

4.1 Therapeutic indications

Zolpidem is indicated for short-term treatment of insomnia in adults in situations where the insomnia is debilitating or is causing severe distress for the patient.

4.2 Posology and method of administration**Paediatric population**

Zolpidem is not recommended for use in children and adolescents below 18 years of age, due to a lack of data to support use in this age group. The available evidence from placebo-controlled clinical trials is presented in section 5.1.

5.1 Pharmacodynamic properties

Paediatric population: Safety and efficacy of zolpidem have not been established in children aged less than 18 years. A randomized placebo-controlled study in 201 children aged 6-17 years with insomnia associated with Attention Deficit Hyperactivity Disorder (ADHD) failed to demonstrate efficacy of zolpidem 0.25 mg/kg/day (with a maximum of 10 mg/day) as compared to placebo. Psychiatric and nervous system disorders comprised the most frequent treatment emergent adverse events observed with zolpidem versus placebo and included dizziness (23.5% versus 1.5%), headache (12.5% versus 9.2%), and hallucinations (7.4% versus 0%) (see sections 4.2).

The UK will maintain the current wording for section 4.3 'In the absence of data, zolpidem should not be prescribed for children' and consequently also the relevant cross-references in sections 4.2 and 5.1.

➤ **Recommendation**

A Type IB variation to be requested from the MAH within 60 days of this report

VI. LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

| MAH | Name of the medicinal product | Strength | Pharmaceutical form | AS |
|------------------------------------|-------------------------------|----------|-----------------------|----------------------|
| SANOFI-AVENTIS PRODUTOS FARMACE | STILNOX | 10 mg | film-coated tablet | ZOLPIDEM TARTRATE |