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SCIENCE MEDICINES HEALTH

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Pharmacovigilance Risk Assessment Committee (PRAC)

Assessment report

For Zolpidem-containing medicinal products

INN: zolpidem

Procedure number: EMEA/H/A-31/1377

Note

Assessment report as adopted by the PRAC and considered by the CMDh with all information of a commercially confidential nature deleted.

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Background information on the procedure

On 04 July 2013, further to evaluation of data resulting from pharmacovigilance activities, the Italian Competent Authority (Agenzia Italiana del Farmaco – AIFA) informed the European Medicines Agency, pursuant to Article 31 of Directive 2001/83/EC, of their consideration of a review of the benefit-risk balance of zolpidem-containing medicinal products indicated for the treatment of short term insomnia, and that it was in the interest of the European Union (EU) to refer the matter to the PRAC.

1. Scientific discussion

1.1. Introduction

Zolpidem is a hypnotic agent authorised for the indication: "Short-term treatment of insomnia".

Zolpidem belongs to the imidazopyridine group of compounds and is structurally unrelated to other hypnotic agents. Zolpidem preferentially binds the omega-1 receptor subtype (benzodiazepine-1 subtype), which corresponds to GABA-A receptors containing the alpha-1 sub-unit, whereas benzodiazepines non-selectively bind both omega-1 and omega-2 subtypes.

In the European Union (EU) member states, zolpidem is available as 5mg and 10mg immediate-release (IR) formulations.

The possibility of drowsiness the day after zolpidem was ingested is a known risk with zolpidem, especially if patients do not sleep for long enough after taking zolpidem, and in the EU the product information (PI) for zolpidem already contains a warning regarding this risk.

In February 2013, the Pharmacovigilance Risk Assessment Committee (PRAC) discussed the results of a search performed by AIFA in EudraVigilance (EV) of cases of impaired driving ability as well as road traffic accidents associated with zolpidem, performed by the AIFA. Following this, the PRAC requested the MAHs of the originator medicinal product for zolpidem to submit a cumulative review of spontaneous cases, clinical studies and published literature of 'impaired driving ability', 'Road traffic accidents' and 'Somnambulism' associated with zolpidem.

In light of the data provided in the cumulative review performed by the MAHs, and taking into consideration the recent Food and Drug Administration (FDA) approved label changes specifying new dosing recommendations for zolpidem-containing medicinal products, AIFA considered that it was in the interest of the EU to refer the matter to the PRAC for a review of zolpidem-containing medicinal products. Therefore in July 2013, AIFA requested the PRAC to give a recommendation under Article 31 of Directive 2001/83/EC on whether marketing authorisation of these products should be maintained, varied, suspended, or withdrawn.

1.2. Clinical safety

1.2.1. Reporting rates

The worldwide reporting rates for impaired driving related events (i.e. 'impaired driving ability', 'road traffic accident', 'sleep driving') and for somnambulism related events ('somnambulism', 'abnormal sleep-related event', 'parasomnia', 'sleep-related eating disorder', 'sleep sex', 'sleep talking" and 'sleep driving') were presented by each of the MAHs for each authorised dosage of zolpidem 5mg and 10mg for the period from 01 January 2003 to 30 June 2013.

The overall reporting rates of the following selected events were significantly higher for the 10mg dosage: 'impaired driving ability', 'road traffic accident', 'sleep driving' related events: 1.69, n= 185

cases per 100 million treatment days, and 'somnambulism': 5.85, n=640 cases per 100 million treatment days. With respect to the 5mg authorised dosage, the reporting rates for 'impaired driving ability', 'road traffic accident', 'sleep driving' related events were: 0.79, n= 26 cases per 100 million treatment days, and 'somnambulism': 2.38, n=78 cases per 100 million treatment days).

This difference was more pronounced for overall "road traffic accident" with reported rates of 1.35 (148 cases per 100 million treatment days) and 0.52 (17 cases per 100 million treatment days) for 10mg and 5mg zolpidem, respectively. The reporting rates of impaired driving and of somnambulism were higher in the 10mg compared to the 5mg dose in the US and Japan. In Europe the reporting rates with the 5mg formulation of zolpidem were higher than with the 10mg formulation (total impaired driving: 0.87 for 5mg vs. 0.27 for 10mg; total somnambulism: 2.17 for 5mg vs. 1.05 for 10mg).

It is noted that the 10mg formulation can be scored to obtain a 5mg dose. This may affect the picture of the reporting rates calculated for both the formulations (overestimation of the use of the 10mg dose and underestimation of the use of the 5mg dose and hence can lead to an underestimation of reporting rates in the 10mg dose and overestimation of the reporting rates in the 5mg dose).

On the basis of the data provided on the reporting rates, the PRAC considered that it could not be concluded that impaired driving or somnambulism occur more frequently with one dose compared to the other. Data stratified by gender was also considered but based on the low number of cases, no sound conclusion could be drawn.

1.2.2. Individual case safety reports

For impaired driving (driving ability) and somnambulism, separate analyses stratified by daily dose of 5mg and 10mg and by gender were submitted. The cases were reported by consumers and healthcare professionals (HCP) - consumers being the main source of reporting - from Europe, the USA, Japan and Australia.

- ***Driving ability***

A total of 236 unsolicited cases of impaired driving were retrieved, corresponding to 30 cases for the 5mg daily dose and 206 cases for the 10mg daily dose. No solicited cases were retrieved.

At a daily dose of 10mg, the distribution of cases was similar in both genders (49.0% in women and 49.5% in men). A higher proportion of adults than elderly reported impaired driving, especially at a daily dose of 10mg: 61.1% in adults and 38.9% in elderly for the 5mg; 86.7% in adults and 13.3% in elderly for the 10mg.

Whatever zolpidem daily dose, most events were serious (23/33 ie 69.7% and 195/264 ie 73.9% at a daily dose of 5 mg and 10 mg respectively) and the most frequently reported serious event was road traffic accident (16/23 ie 69.6% and 125/195 ie 64.1% at a daily dose of 5 mg and 10 mg respectively). The number of non-serious cases tended to be higher in female (n=27) than in male (n=18). Conversely, the number of serious cases tended to be slightly higher in male (n = 76) than in female (n = 72). Whatever the seriousness, most of the events were reported at a 10 mg daily dose (48/53 ie 90.6% for non-serious events and 195/218 ie 89.4% for serious events). The beginning of treatment was the most risky period with 40.0% and 13.2% of the cases occurring within the first treatment day for 5mg and 10mg respectively. At the daily dose of 5 mg and 10 mg respectively, 27.3% (3/11) and 9.7% (6/62) of the patients experienced impaired driving within the following 4 hours after the last zolpidem intake.

- ***Somnambulism***

A total of 1036 cases (1034 unsolicited, 2 solicited) were retrieved, including 100 cases reported at 5mg daily dose and 936 cases reported at 10mg daily dose. The two solicited cases were non-serious and reported at a 10mg daily dose; no causality assessments were available.

At a daily dose of 10mg, the distribution of cases was similar in both genders: 89.7% in men and 90.6% in women cases. At a daily dose of 10 mg, more adults than elderly patients experienced somnambulism (71.1% in adults versus 28.6% in elderly). At a daily dose of 5 mg, the distribution of cases was similar in adults and in elderly (47.4% and 51.3% respectively).

Whatever zolpidem daily dose, most events were non-serious (88/116 i.e. 75.9% and 782/1171 i.e. 66.8% at a daily dose of 5 mg and 10 mg respectively) and the most frequently reported serious event was somnambulism (13/14 i.e. 92.9% and 125/167 i.e. 74.9% at a daily dose of 5 mg and 10 mg respectively). Whatever the seriousness, most of the events were reported at a 10 mg daily dose (782/870 i.e. 89.9% for non-serious events and 167/181 i.e. 92.3% for serious events). The most risky periods were the first treatment day (20.6% and 21.2% of the cases for 5mg and 10mg respectively) and after 3 months of use (55.9% and 44.8% of the cases for 5mg and 10mg respectively). At the daily dose of 5 mg and 10 mg respectively, 11.1% (1/9) and 29.9% (46/154) of the patients experienced somnambulism within the following 4 hours after the last zolpidem intake.

- ***Risk factors***

Overall, whatever zolpidem daily dose and the type of reactions (impaired driving or somnambulism), the most frequently reported risk factor was concomitant intake of other CNS depressants, and in particular antidepressants such as SSRIs (for impaired driving: 8/30 ie 26.7% and 80/206 ie 38.9% at a daily dose of 5 mg and 10 mg respectively; for somnambulism: 28/100 ie 28.0% and 292/936 ie 31.2% at a daily dose of 5 mg and 10 mg respectively).

At a daily dose of 5 mg, 16.7% (5/30) and 9.0% (9/100) of the patients who experienced impaired driving or somnambulism respectively were also treated with antiepileptics.

At a daily dose of 10 mg, 15.0% (31/206) and 10.4% (97/936) of the patients who experienced impaired driving or somnambulism respectively were also treated with narcotic analgesics.

For impaired driving, other risk factors included sleep-related abnormal behaviours (11/30 ie 36.7% and 129/206 ie 62.6% at a daily dose of 5 mg and 10 mg respectively), while for somnambulism, other risk factors included sleep deprivation and alcohol or illicit drugs consumption (7/100 ie 7.0% and 41/936 ie 4.4% at a daily dose of 5 mg and 10 mg respectively).

1.2.3. Literature

A comprehensive literature search for articles reporting or discussing zolpidem and impaired driving ability and/or road traffic and somnambulism and/or related disorders was performed (covering the period from 1999 up to July 2013).

Driving simulation studies

The experimental studies performed to assess the impairment associated with the use of sleep medications including zolpidem were submitted. These studies assessed driving performance in the next morning after intake of drugs either at bedtime or in the middle of the night.

In studies evaluating bedtime intake, zolpidem was not associated with impaired driving performance on the next morning (Leufkens 2009[1], Otmani 2008[2], Staner 2005[3]).

[1] Leufkens TR, Lund JS, Vermeeren A. Highway driving performance and cognitive functioning the morning after bedtime and middle-ofthe- night use of gaboxadol, zopiclone and zolpidem. J Sleep Res. 2009;18:387–96.

In studies evaluating middle of the night intake of zolpidem, the results are inconsistent with some studies showing mainly modifications of lateral position (Bocca 2011[4], Meskali 2009[5], Leufkens 2009[2], Partinen 2003[6], Verster 2002[7]), and other studies showing no impairment (Bocca 1999[8], Berthelon 2003[9]).

Epidemiological studies assessing the risk of road traffic accidents

The submitted epidemiological studies that specifically focussed on assessing the impact of zolpidem use on road-traffic accidents provided inconsistent results:

- no increase of risk of road traffic accidents associated with the use of zolpidem as recommended (Orriols 2011[10]), or with short term use of zolpidem (less than 4 weeks) (Gibson 2009[11]);
- increase of risk of road traffic accidents associated with high consumption of zolpidem (more than one pill per day) (Orriols 2011[13]), with the use of zolpidem the day before the accident (Yang 2011[12]), in the first week after filling the prescription mainly in men users (Gustavsen 2008[13]);

In these epidemiological studies, the risk of accident may be related to unmeasured use of alcohol and other psychotropic medications, and confounding by indication cannot be ruled out. Moreover in these studies, there was no information on the exact dose and timing of zolpidem intake.

Complex sleep behaviours and other sleep related problems

Complex sleep behaviours and sleep related disorders have been reported as rare events in zolpidem users; the three main types described in the literature included somnambulism, sleep related eating disorder and sleep-driving (Hoque *et al*., 2009[14]).

Recent reviews summarised case reports of sleepwalking in zolpidem users (Inagaki *et al*., 2010[15]; Wu-Chou *et al*., 2012[16]). Hwang *et al*.[17] found that risk predictors of complex sleep behaviours were

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[2] Otmani S, Demazières A, Staner C, Jacob N, Nir T, Zisapel N et al. Effects of prolonged release melatonin, zolpidem, and their combination on psychomotor functions, memory recall, and driving skills in healthy middle aged and elderly volunteers. Hum psychopharmacol.2008;23(8):693-705.

[3] Staner L, Ertle S, Boeijinga P et al. Next-day residual effects of hypnotics in DSM-IV primary insomnia: a driving simulator study with simultaneous electroencephalogram monitoring. Psychopharmacology. 2005;181:790-8

[4] Bocca ML, Marie S, Lelong-Boulouard V, Bertran F, Couque C, Desfemmes T, Berthelon C et al. Zolpidem and zopiclone impair similarly monotonous driving performance after a single nighttime intake in aged subjects. Psychopharmacology 2011;214(3):699-706

[5] Meskali M, Berthelon C, Marie S, Denise P, Bocca ML. Residual effects of hypnotic drugs in aging drivers submitted to simulated accident scenarios: an exploratory study. Psychopharmacology (Berl). 2009;207(3):461-7

[6] Partinen M, Hirvonen K, Hublin C, Halavaara M, Hiltunen H. Effects of after-midnight intake of zolpidem and temazepam on driving ability in women with non-organic insomnia. Sleep Medicine 2003 ;4:553–561

[7] Verster J.C., Volkerts E.R., Schreuder A.H.C.M.L., Eijken E.J.E., Van Heuckelum J.H.G., Veldhuijzen D.S., Verbaten M.N., Paty I., Danjou P., Patat A., Darwish M. Journal of Clinical Psychopharmacology 2002;22(6):576-83.

[8] Bocca ML, Le Doze F, Etard O, Pottier M, L'Hoste J, Denise P. Residual effects of zolpidem 10mg and zopiclone 7.5mg versus flunitrazepam 1mg and placebo on driving performance and ocular saccades. Psychopharmacology 1999;143(4):373-9

[9] Berthelon C, Bocca ML, Denise P, Pottier A. Do zopiclone, zolpidem and flunitrazepam have residual effects on simulated task of collision anticipation? J Psychopharmacol 2003;17(3):324–31

[10] Orriols L, Philip P, Moore N, Castot A, Gadegbeku B, Delorme B, Mallaret M, Lagarde E. Benzodiazepine-like hypnotics and the associated risk of road traffic accidents. Clin Pharmacol Ther. Apr 2011; 89(4):595-601

[11] Gibson JE, Rubbard RB, Smith CFP, Tata LJ, Britton JR, Forgarty AW. Use of selfcontrolled analytical techniques to assess the association between use of prescription medications and the risk of motor vehicle crashes. Am J Epidemiology 2009; 169: 761-768

[12] Yang YH, Lai JN, Lee CH, Wang JD, Chen PC. Increased risk of hospitalization related to motor vehicle accidents among people taking zolpidem: a case-crossover study. J Epidemiol. 2011;21(1):37-43

[13] Gustavsen I, Bramness JG, Skurtveit S, Engeland A, Neutel I, Mørland J. Road traffic accident risk related to prescriptions of the hypnotics zopiclone, zolpidem, flunitrazepam and nitrazepam. Sleep Med. 2008; 9(8): 818-22

[14] Hoque R, Chesson AL Jr. Zolpidem-induced sleepwalking, sleep related eating disorder, and sleep-driving: fluorine-18-flourodeoxyglucose positron emission tomography analysis, and a literature review of other unexpected clinical effects of zolpidem. J Clin Sleep Med. 2009 Oct15;5(5):471-6.

[15] Inagaki T, Miyaoka T, Tsuji S, Inami Y, Nishida A, Horiguchi J. Adverse reactions to zolpidem: case reports and a review of the literature. Prim Care Companion J Clin Psychiatry. 2010;12(6)

[16] Wu-Chou A.I., Shen W.W., Shen W.W. Complex behaviors related to zolpidem: An analysis of published clinical cases from Taiwan. Journal of Experimental and Clinical Medicine 2012;4(2):113-118

younger users, women users, higher dosage users, and not going to sleep immediately after taking zolpidem.

Cases of sleep-related eating disorders have been reported with zolpidem users, either individual cases as summarised by Nzwalo *et al.,* 2013[18] or reports of case series (Valiensi *et al.,* 2010[19]; Schenck *et al*., 2005[20]). A prospective cohort of patients with sleep-related eating disorders evaluated for the main clinical features of preference of high-energy food and amnestic features associated with complex automatism, was shown to support the association of zolpidem and sleep-related eating disorders[21].

Cases of sleep driving were characterised by poor motor control and confusion associated with amnesia. Risk factors include the concomitant ingestion of other sedating drugs, a higher dose of zolpidem, a history of parasomnia, ingestion at times other than bedtime or when sleep is unlikely, poor management of pill bottles, and living alone (Poceta *et al*., 2011[1]).

Risk of impaired driving ability after re-administration of zolpidem in the middle of the night

Of the publications mentioned above, about 8 studies included middle-of-the-night intake of 10mg zolpidem. Six of these 8 studies showed impaired driving ability after night time administration of zolpidem, or when zolpidem was administered less than 8 hours prior to taking the driving ability test suggesting that night time administration increases the risk of motor vehicle accidents.

Concomitant drug administration

In the literature, concomitant sedating medications were reported to be risk factors for zolpidem-associated automatisms and parasomnias[22].

In addition Hesse *et al*. summarised in 2003 the data about the potential interactions of zolpidem and a clinically a very likely important interaction regarding enhanced sedative effects (delayed recall, decreased alertness) by concomitant use of zolpidem with ketoconazole or cimetidine was reported.

Vlase et al.[23] evaluated a possible pharmacokinetic interaction between zolpidem and ciprofloxacin /carbamazepine /fluvoxamine in healthy volunteers. They concluded that ciprofloxacin interacts with zolpidem in healthy volunteers, raising its bioavailability by about 46%. This magnitude of effect is likely to be clinically significant. Experimental data has also shown a pharmacokinetic interaction between zolpidem and fluvoxamine, suggesting that the observed interaction might be clinically significant[24].

[17] Hwang TJ, Ni HC, Chen HC, Lin YT, Liao SC. Risk predictors for hypnosedative-related complex sleep behaviors: a retrospective, cross-sectional pilot study. J Clin Psychiatry. 2010 Oct;71(10):1331-5
[18] Nzwalo H, Ferreira L, Peralta R, Bentes C. Sleep-related eating disorder secondary to zolpidem. BMJ Case Rep. 2013 Feb 21;2013
[19] Valiensi SM, Cristiano E, Martínez OA, Reisin RC, Alvarez F. [Sleep related eating disorders as a side effect of zolpidem]. Medicina (B Aires). 2010;70(3):223-6. (english translation of Spanish)
[20] Schenck CH, Connoy DA, Castellanos M, et al. Zolpidem-induced sleep-related eating disorder (SRED) in 19 patients. Sleep 2005;28:A259
[21] Wing YK, Lam SP, Li SX, Zhang J, Yu MW. Sleep-related eating disorder and zolpidem: an open interventional cohort study. J Clin Psychiatry. 2010 May;71(5):653-6
[22] Poceta JS. Zolpidem ingestion, automatisms, and sleep driving: a clinical and legal case series. J Clin Sleep Med 2011;7(6):632–8.
[23] Vlase L, Popa A, Neag M, Muntean D, Leucuţa SE: Pharmacokinetic interaction between zolpidem and ciprofloxacin in healthy volunteers. Eur J Drug Metab Pharmacokinet. 2011 Jan;35(3-4):83-7. doi: 10.1007/s13318-010-0014-9.
[24] Vlase L, Popa A, Neag M, Muntean D, Achim M, Leucuţa SE: Effect of fluvoxamine on the pharmokinetics of zolpidem: a two-treatment period study in healthy volunteers. Clin Exp Pharmacol Physiol. 2012 Jan;39(1):9-12.

Driving under the Influence of Drugs, Alcohol and Medicines (DRUID) report

The recommendations from a project funded by the European Commission – DRUID (part of the 6th Framework Programme), which was aimed at assessing and reducing the influence of drugs and medication on the risk of driving was also taken into account.

With respect to Zolpidem the DRUID group recommends the following:

1. Inform the patient about the effects of the medicine on reaction time and that the medication can cause side effects that impair driving (dizziness, drowsiness, sleepiness, blurred/double vision and reduced alertness).
2. Advice the patient not to drive for the first 8 hours after taking the medicine and also to be careful in other situations (e.g. using machinery and working at heights).
3. Advice the patient not to drink alcohol or use other psychoactive substances when taking this medicine.

1.2.4. EMA drug utilisation study (DUS)

The results from an EMA drug utilisation study using IMS Health electronic health records in the primary care setting in 2012 are also summarised below. Three IMS databases from Germany (DE), France (FR) and the United Kingdom (UK) were used for the analysis. The objective of the study was to estimate zolpidem use stratified by gender and age.

The results showed that zolpidem was more often prescribed to women; i.e. 66.7% in Germany, 65.3% in the United Kingdom and 62.9% in France. Around 35-40% of men and women were zolpidem users 65 years of age and older in FR and UK. In DE, the proportion older than 65 years was much larger; 58% of men and 66% of women were 65 years of age and older.

The interpretation of the results is hampered by the lack of evidence that all groups are at risk in the same extent (e.g. comparable participation in road traffic). The use of low strength (5mg) and high strength (10mg) prescribing was also estimated based on the dose information provided by the prescriber. If the information was missing the dose calculated was based on the strength, pack size and duration of prescription. The numbers of patients stratified by prescribed dose of zolpidem, showed that the number of patients where dose information is missing or could not be calculated varied from around 90% in DE to around 30% in FR and less than 5% in UK.

1.2.5. Overall discussion on safety

The analysis of the individual case reports of driving ability and somnambulism submitted showed that whatever the age and gender category, most of the cases of impaired driving were reported at a 10mg daily dose for both events. These results could be explained by significantly higher exposure rates for 10mg formulation.

Although post marketing data showed that more cases had been reported in women than in men at a 5mg daily dose, a similar number of cases were reported at a 10mg daily dose in these two groups of patients. Taking into consideration the limitations of spontaneous reporting, e.g. underreporting, gender differences in the willingness to report – these data are to be interpreted cautiously and do not point towards an increased risk for women compared to men. Of note, the EMA DUS showed that zolpidem was more often prescribed to women compared to men.

It was observed from post-marketing data that concomitant use of CNS depressant drugs (including the newer antidepressants, antiepileptics, antipsycotics, hypnotics, anxiolitics, narcotic analgesics, anaesthetics and sedative antihistaminics) was the main risk factor for somnambulism and impaired

driving. This was supported by a literature review that showed that concomitant administration of chlorpromazine, imipramine, other antidepressants and ketoconazole can increase sedative effect of zolpidem, which may result in impaired driving ability, and may lead to a road traffic incident. It was also shown that pharmacodynamic interaction can develop by concomitant use of zolpidem and SSRI (selective serotonin re-uptake inhibitor) agents, resulting in altered mental status. Alcohol or illicit drugs consumption was also listed as a risk factors for these events.

The results of epidemiological studies related to the association between the use of zolpidem and the risk of accident were inconsistent. Other published studies showed an association between middle of the night intake and impaired driving performance on the next morning but an association between bedtime intake of zolpidem and impaired driving performance was not found. Finally, the DRUID recommendations stating that the risk of dizziness, drowsiness, sleepiness, blurred/double vision and reduced alertness could impair driving, and recommending a resting period of 8 hours after taking zolpidem, as well as not drinking alcohol or using psychoactive substances when taking zolpidem, were noted.

1.3. Pharmacokinetic-Pharmacodynamic relationship

Considering the safety concerns associated with the use of zolpidem and the suggestion that a dose reduction may be appropriate to mitigate the risk of impaired driving, somnambulism and road traffic accidents, the PRAC requested the MAHs to present any relevant evidence on the PK-PD relationship across dose levels (5mg and 10mg) including in special populations.

A number of studies have investigated zolpidem pharmacokinetic (PK) or pharmacodynamic (PD) in healthy subjects and patients, but PK-PD relationships are rarely described. Six publications concerning PK-PD relationships were presented and considered in this review.

Only one publication directly assessed PK-PD relationships between zolpidem 5mg and 10mg dose levels, (Richens *at al* 1993[25]). In this publication only small differences in the pharmacodynamic variables (saccade velocity, Critical flicker fusion threshold (CFFT), five choice serial reaction time and mood) were observed.

In the other studies, the pharmacodynamics were compared with other medicinal products or 10 and 20mg of zolpidem. Two publications used zolpidem (10mg and 20mg) as a comparator to another sedative hypnotic medication (Greenblat *et al.,* 1998[26], Drover *et al*., 2000[27]). Three publications assessed PK-PD relationships at the 10mg dose level (Allain *et al.,* 1995[28], De Hass *et al.,* 2010[29], Greenblatt *et al.,* 2000[30])

[25] Richens A, Mercer A, Jones D, Griffiths A, Marshall R. Effects of zolpidem on saccadic eye movement and psychomotor performance: a double blind, placebo controlled study in healthy volunteers. Br J Clin Pharmac. 1993;36:61-65.
[26] Greenblatt D, Harmatz J, Von Moltke L, Ehrenberg B, Harrel L, Corbett K, Counihan M, Graf J, Darwish M, Mertzanis P, Martin P, Cevallos W, Shader R. Comparative kinetics and dynamics of zaleplon, zolpidem, and placebo. Clin Pharmacol Ther. 1998;64(5):553-561
[27]Drover D, Lemmens H, Naidu S, Cevallos W, Darwish M, Stanski D. Pharmacokinetics, pharmacodynamics, and relative pharmacokinetic/pharmacodynamic profiles of zaleplon and zolpidem. Clin Ther. 2000;22(12):1443-1461.
[28] Alain A, Patat A, Lieury A, Le Coz F, Janus C, Menard G, Gandon J. Comparative study of the effects of zopiclone (7.5mg), zolpidem, flunitrazepam and a placebo on nocturnal cognitive performance in healthy subjects, in relation to pharmacokinetics. Eur Psychiatry. 1995;10(Suppl 3):129s-135s.
[29] De Hass S, Schoemaker R, Van Gervan J, Hoever P, Cohen A, Dingemanse J. Pharmacokinetics, pharmacodynamics and the pharmacokinetic/pharmacodynamic relationship of zolpidem in healthy subjects. J Psychopharmacol. 2010;24:1619-1628.
[30] Greenblatt D, Harmatz J, Von Moltke L, Wright C, Durol A, Harrel-Joseph L, Shader R. Comparative kinetics and response to the benzodiazepine agonists triazolam and zolpidem: evaluation of sex-dependent differences. J Pharmacol Exp Ther. 2000;293:435-443.

Overall, it can be concluded from the submitted literature, that there is a dose dependency PK/PD relationship for most pharmacodynamic variables. This is described in the article of De Hass *et al*[29], where the results of a PK/PD model for zolpidem based on a study in healthy men volunteers was described. The conclusion was that the pharmacodynamic variables like saccadic and smooth pursuit eye movements, visual analogue score (VAS) of alertness, body sway, pharmaco-electroencephalogram (EEG) and adaptive tracking were associated with a quick rise in plasma levels of zolpidem.

With respect to the persistence of the effects of zolpidem, in most studies the pharmacodynamic effects returned to baseline 8 hours after intake of the product. However, most studies were conducted in small numbers of healthy men/women subjects.

Special populations

The impact of gender, age, weight, liver or renal impairment and race on zolpidem pharmacokinetics were reviewed in the literature.

Pharmacokinetic data indicated that women achieve approximately 45% higher plasma exposure of zolpidem than men (both Cmax and AUC). Approximately half the difference between men and women was accounted for by differences in weight that result in women receiving a marginally higher mg/kg dose. The remaining difference (approximately 25%) was not statistically significant.

Studies in populations ranging in age from 8 to 95 years have shown that clearance in children is 3 times greater than in young adults, resulting in similar exposure despite higher doses, on a mg/kg basis, in children. In elderly subjects, zolpidem exposure is significantly increased and clearance is significantly decreased compared to younger subjects. In elderly patients, the initial recommended dose is 5mg/day.

Pharmacokinetic data also indicated that Cmax was lower in the obese individuals probably due to a smaller dose in terms of mg/kg, and larger volume of distribution. Absorption was slower and half-life and AUC were slightly greater for the obese individuals. Overall, the pharmacokinetic data for obese people are not sufficiently different from people of normal body weight to require dose adjustment.

Hepatic impairment is associated with a 2-fold increase in Cmax, a 5-fold increase in AUC and a 3-fold increase in elimination half-life compared to healthy adults. However, the onset of drowsiness and duration of action of a given dose were not different from those observed in healthy individuals. In patients with hepatic impairment, the initial recommended dose is 5mg/day.

Patients undergoing haemodialysis eliminate zolpidem more slowly and exposure (AUC) is increased by 20% compared to healthy adults. In patients with long term renal insufficiency who were not yet undergoing haemodialysis, AUC increased by 60% and elimination half-life was approximately doubled. Although the exposure of zolpidem is moderately increased in patients with renal insufficiency compared to healthy adults, dosage adjustment is generally not required.

Race was not associated with important differences in zolpidem pharmacokinetic parameters.

1.4. Clinical efficacy

As part of this referral procedure, the MAHs were requested to provide all available data on the efficacy of the 5 mg and 10 mg dosages from clinical studies and all other available data sources, in particular data on the direct comparison between the efficacy of the 5 mg and the 10 mg dosage stratified by gender.

1.4.1. Randomised controlled clinical trials (RCTs)

Adults

Altogether 19 studies were included in the development program for Zolpidem. These included seven pivotal studies and 12 supportive studies. All seven studies were double-blind RCTs with either a parallel-group or cross-over design. Of these seven studies, three were dose-finding studies starting with 5mg of zolpidem. The remaining four pivotal and the additional 12 supportive studies included doses of 10mg or higher and are therefore not presented here.

The results of the three dose finding studies are summarised below:

Study MR113 (published by Roth *et al*., 1995)[31] was a randomised, double-blind, placebo-controlled trial which investigated five doses (5mg, 7.5mg, 10mg, 15mg and 20mg) of zolpidem in 462 non-elderly healthy volunteers with transient insomnia using polysomnography (PSG). Subjects slept in a sleep laboratory for one night.

The results showed that 7.5mg and 10mg zolpidem produced statistically significant improvement on all PSG efficacy parameters, while the 5mg, 15mg, and 20mg doses produced a milder and non-statistically significant effect. An optimal effect was seen at doses of 7.5mg and 10mg.

For latency to persistent sleep (LPS), the primary parameter of efficacy, the difference from placebo for the 5mg dose was small and not statistically significant in both men (3.1 [-6.7, 13.0] minutes) and women (2.9 [-13.1, 19.1] minutes). Higher latencies were achieved in the higher doses. Specifically, for the 10mg dose the difference form placebo was 10.1 (3.5, 16.5) minutes in men and 8.0 (-8.9, 24.9) minutes in women.

The results of the post-hoc analysis for evaluating gender effects on efficacy which were presented showed that when assessing LPS, sleep efficiency, subjective total sleep time, wake time during sleep and number of awakenings there were no gender effects on the treatment efficacy and hence no suggestion that 5mg may be more effective in women.

ANOVA analyses of the relationship between weight and efficacy (on latency to persistent sleep), stratified by gender were also provided. The results suggested that the gender differences were not due to weight differences, since adjustment for weight did not change the gender effect.

Study MR114 was a single-centre, double-blind, randomised, placebo-controlled study performed to evaluate zolpidem 5mg, 10mg, 15mg, and 20mg and placebo. The subjects were healthy volunteers aged 18-60 years not having slept in a sleep laboratory before. Altogether 34 subjects were randomised to treatment. Efficacy on sleep was evaluated by PSG, sleep questionnaires, psychomotor tests, and daytime sleep latency tests.

The results showed a mixture of significant and mainly non-significant effects on various sleep parameters. The design of the study does not allow a direct comparison between the 5mg and the 10mg treatments. In addition, since only 2 of the 34 subjects were women in this study, a stratified analysis by gender was not conducted.

Study MR115 was a randomised, double-blind, multicentre, placebo-controlled study designed to compare the hypnotic efficacy and safety of 5mg, 10mg, and 20mg of zolpidem versus placebo in 114 non-elderly adult outpatients (71 women, 43 men) with chronic insomnia. Patients spend night 1 and 2 in the sleep laboratory, nights 3-7 at home and night 8 again in the sleep laboratory. Sleep parameters were measured with a PSG and via questionnaires.

[31] Roth T, Roehrs T, Vogel G. Zolpidem in the treatment of transient insomnia: a double-blind, randomized comparison with placebo. Sleep. 1995 May; 18 (4): 246-51.

Using PSG the effects on latency to persistent sleep for the 5mg group were statistically superior to placebo (p=0.024) in the 1st night of treatment. However on the 7th night, lack of statistical significance in the 5mg group was observed, and it may have been partly due to a numerically smaller effect and a larger standard error (SE) in this group (compared to the 10mg and 20mg treated group). It is also noted that baseline efficacy values in the 5mg treated group were higher compared to the other groups. It was clarified by the MAH that this large variability was driven by a high value at baseline for one of the women patients.

The results of the post-hoc analysis for evaluating gender effects on efficacy which were presented and altogether, efficacy results of study MR115 provided only weak and inconsistent support for an interaction between gender and treatment. For the primary endpoint (LPS) better efficacy in response to the 5mg dose in women was seen only in night 2 but not in night 8.

At night 2, the mean difference from placebo with the 5mg dose was 9.5 (-45.8, 64.8) min in men, and 17.0 (-17.7, 51.7) min in women. It is noted that in women the effect of the 5mg was larger than of the 10mg: 17.0 for 5mg 9.4 for 10mg. In men, however, the effect of the 5mg was less than that of the 10mg: 9.5 for 5mg and 41.5 for 10mg.

For LPS at night 8, the difference from placebo in the 5mg dose was 17.8 (-30.5, 66.2) min in men and 18.7 (-24.2, 61.6) min in women. At this time point the effect of the 10mg was higher than that of the 5mg for both men and women 44.5 (-5.0 , 94.0) in men and 32.7 (0.5 , 64.9) in women. In addition, there was no gender difference in the response to the 5mg dose.

For the secondary efficacy (sleep) parameters, only subjective total sleep suggested efficacy of the 5mg in women while the other parameters (sleep efficiency and wake time during sleep) did not.

Elderly

Thirteen studies evaluating zolpidem in the elderly population were submitted. This included 4 pivotal studies and 9 supportive studies. All 4 pivotal RCTs in the elderly included zolpidem 5mg and were double-blind with either a parallel group or cross-over design. The lower age limit was 60 years in three of four studies and the mean ages in all 4 studies were greater than 65 years.

Altogether the majority of the studies in the elderly demonstrated efficacy of zolpidem 5mg, and therefore support the dose of 5mg currently recommended in this age group.

1.4.2. Literature data

A total of 15 published studies were identified in the literature (cut-off date July 17, 2013). Except for the study by Roth et al. (1995)[31] which investigated five doses, all studies that were identified included only zolpidem at the doses of 10mg or 15mg. Generally, the results of these studies confirmed the efficacy of Zolpidem 10mg in non-elderly adult patients with primary insomnia.

One published systematic review of efficacy clinical trials with zolpidem (identified from a literature search) by Priest et al. (1997) in patients with insomnia covered more than 50 international clinical trials published since 1986. The studies included different patient populations including normal volunteers, general practice outpatients and psychiatric out- or in-patients with varying sleep disorders; both transient and chronic. Assessment methods used included objective and subjective measures of hypnotic efficacy for different treatment durations. Zolpidem 10mg was shown to be superior in most trials on sleep parameters such as total sleep time, sleep onset latency and nocturnal awakenings. Zolpidem maintained normal sleep physiology and the authors concluded that 10mg was the recommended dose for the short-term treatment of insomnia in the non-elderly. It was also

concluded that Zolpidem 5mg was had been shown to be effective at inducing sleep in elderly patients whilst giving an optimum safety profile.

Literature data were also presented of placebo-controlled studies in patients with nonorganic insomnia, short-term insomnia and in experienced travellers experiencing jet lag from transatlantic travel (crossing 5 to 9 time zones). Zolpidem 10mg was found to be more effective than placebo in these studies.

The effect of continuous vs. intermittent administration of zolpidem 10mg was evaluated in patients with chronic insomnia treated for 2 weeks with zolpidem 10mg, either continuously or intermittently. The results suggest that the efficacy of zolpidem 10mg is comparable whether administered every night or intermittently (Lahmeyer et al. 1997).

In patients who had persistent insomnia in the presence of effective and stable antidepressant treatment with the SSRIs fluoxetine (≤40mg/day), sertraline (≤100mg/day) or paroxetine (≤40mg/day) for DSM[32]-IV major depressive disorder, dysthymic disorder or minor depressive disorder, zolpidem 10mg was effectively and safely co-administered with an SSRI, resulting in improved self-rated sleep, daytime functioning and well-being[33].

1.4.3. Overall discussion on efficacy

Available evidence from randomised clinical trials MR113, MR114 and MR115 confirmed the efficacy of zolpidem 10mg dose in the approved indication. Regarding the 5mg dose, the evidence provided suggested that this dose is less effective compared to the 10mg in the overall population. However, the 5mg dose of zolpidem was shown to be effective in some patients, such as in the elderly population.

Only weak and inconsistent support for an interaction between gender and treatment could be observed from the efficacy results of study MR115. No support for an interaction between dose and gender was evident from the results of study MR113, and no conclusion could be drawn from study MR114. Hence the stratification by gender of the presented results did not show signals of significant heterogeneity of the efficacy parameters across gender. In addition, the results suggested that weight differences between men and women do not explain the potential gender difference and that weight adjusted dose is not related to the outcome, hence dose adjustment based on weight is not considered necessary.

1.5. Overall benefit-risk assessment

The PRAC reviewed the safety and efficacy data relating to the risk of impaired driving and somnambulism following treatment with zolpidem.

The analysis of the submitted individual case reports of driving ability and somnambulism showed that whatever the age and gender category, most of the cases of impaired driving were reported at a 10mg daily dose for both events. Amongst the risk factors for impaired driving and somnambulism were, concomitant intake of other CNS depressants, sleep-deprivation and alcohol or illicit drugs consumption. Discrepancies about drug-drug interactions information were observed in different product information of zolpidem containing products, notably on the interaction of zolpidem with CNS

[32] Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, a manual published by the American Psychiatric Association (APA) that includes all currently recognized mental health disorders, and are used by mental health professionals to describe the features of a given mental disorder and indicate how the disorder can be distinguished from other, similar problems

[33] Asnis GM, Chakraburty A, DuBoff EA, Krystal A, Londborg PD, Rosenberg R, Roth-Schechter B, Scharf MB, Walsh JK. Zolpidem for persistent insomnia in SSRI-treated patients. J Clin Psychiatry 1999 October 60 (10); 668-676

depressant. Based on evidence from the literature, it was considered necessary to amend and harmonise the 'Interaction with other medicinal products' section of the product information.

The analysis of driving simulation studies showed an association between impaired driving performance on the next morning and middle of the night intake of zolpidem. It was therefore considered by the PRAC that the dosing recommendation should include instructions that Zolpidem is to be taken in a single intake immediately at bedtime and should not be re-administered during the same night.

Considering that the effect of zolpidem may last for at least 8 hours and in view of the above referred risk factors, the PRAC also recommended to include warnings indicating that the risk of impaired driving is increased if zolpidem is taken within less than 8 hours before performing activities that require mental alertness, if zolpidem is taken in a higher than the recommended dose, and/or co-administered with other CNS depressants, and/or alcohol or illicit drugs.

With regards to the effects on the ability to drive and use machines, the PRAC recommended that vehicle drivers and machine operators are warned that in addition to the possible risk of drowsiness, prolonged reaction time and impaired driving the morning after therapy, there is also the possibility of dizziness, sleepiness, blurred/double vision and reduced alertness. The product information was amended accordingly.

Finally and in view of further minimising the risks of impaired driving and somnambulism, a potential lowering of the recommended dose for adults was discussed by the PRAC. However, on a population level, the randomised trials only showed convincing evidence of efficacy of the 10mg dose of zolpidem. The provided data did not consistently show that a lower dose would be effective or that a lower dose would significantly reduce the risk of impaired driving and somnambulism, and it was considered that reducing the daily recommended dose would likely result in in-effective doses being used, in turn resulting in additional doses being taken in the middle of the night and in an increased risk of accidents the following day.

The PRAC therefore agreed that the recommended daily dose of zolpidem should not be reduced for adults. It was however acknowledged that in some patients a lower dose of 5mg could be effective. The currently recommended daily dose in the elderly and in patients with hepatic impairment is 5mg, and this dose recommendation remains unchanged in the product information.

Based on these conclusions, the PRAC concluded that the benefit-risk balance of zolpidem-containing medicinal products remains favourable subject to the agreed changes to the product information.

1.6. Changes to the product information

The PRAC recommended that amendments be introduced in the Summary of Product Characteristics (SmPC) to the following sections 4.2, 4.4, 4.5 and 4.7 as follows:

- An amendment of section 4.2 which includes a recommendation that zolpidem should be taken as a single intake immediately at bedtime, not to be re-administered and that the total daily dose must not exceed 10mg.
- A warning in section 4.4 indicating that the risk of impaired driving is increased if zolpidem is taken with less than 8 hours before performing activities that require mental alertness, a higher than the recommended dose or co-administration with other CNS depressants or alcohol or illicit drugs. Zolpidem should be taken in a single intake immediately at bedtime and not be re-administered during the same night.
- A warning in section 4.5 against concomitant use with CNS depressants and CYP450 inhibitors and inducers.

- A revision of section 4.7 regarding including (in addition to drowsiness, impaired driving and prolonged reaction time the morning after therapy) dizziness, sleepiness, blurred/double vision and reduced alertness.
- An addition to section 5.1 of the efficacy results from two randomised double-blind studies of the mean time to fall asleep following administration of 5mg and 10mg of zolpidem.

Corresponding changes to the package leaflet have also been introduced.

2. Overall conclusion and grounds for the recommendation

Whereas

- The PRAC considered the procedure under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data for zolpidem-containing medicinal products;
- The PRAC reviewed all available data provided by the MAHs on the safety and efficacy of zolpidem-containing medicines with regards the risk of impaired driving ability and somnambulism following treatment with zolpidem;
- The PRAC considered that the data from post-marketing spontaneous case reports, clinical trials, published literature and other available information have shown that the use of zolpidem-containing products is associated with an increased risk of impaired driving and somnambulism;
- The PRAC also reviewed the available data on the efficacy of zolpidem in order to determine whether amendments to the posology would help to minimise the risks but agreed that the available efficacy data do not provide robust evidence that a lower dose would be effective on a population level;
- The PRAC considered that the above-mentioned risks of impaired driving ability and somnambulism could be mitigated by changes to the product information of zolpidem-containing medicines, in particular that zolpidem should be taken as a single intake immediately at bedtime and not exceed the recommended dose, without being re-administered during the same night, as well as highlighting the risks regarding impaired driving and somnambulism, warnings and precautions aimed at decreasing this risk and also the risks of co-administration with CNS depressants and alcohol, and/ or illicit drugs;

the PRAC, as a consequence, concluded that the benefit-risk balance of the medicinal products containing zolpidem remains favourable, subject to the agreed changes to the product information.

Having considered the matter, the PRAC therefore recommended the variation of the marketing authorisations for zolpidem -containing medicinal products.

The divergent position is appended to the PRAC recommendation.

Appendix 1

Divergent position to PRAC recommendation

Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data

Procedure No: EMEA/H/A-31/1377

Zolpidem-containing medicinal products

Divergent statement

The following PRAC member considers that the benefit-risk balance of zolpidem is not favourable based on the following grounds:

Clinical efficacy data are limited to support the 5 mg dose. However, even though the 5 mg is associated with inadequate efficacy on average at a population level, inter-individual variability can lead to propose a recommending starting dose at 5 mg on an individual basis level. Therefore the pharmacokinetics of zolpidem are influenced by a number of factors (gender, age, hepatic impairment). The submitted PK evidence in this procedure suggests slower clearance of zolpidem in women: young females achieve approximately 45% higher plasma exposure of zolpidem than males (both Cmax and AUC). Also, according to FDA submitted data, driving simulation and laboratory studies indicate that zolpidem blood levels above approximately 50 ng/mL appear capable of impairing driving to a degree that increases the risk of a motor vehicle accident. In pharmacokinetic trials of 10 mg Ambien (or bioequivalent zolpidem products) that included approximately 250 men and 250 women, about 15% of women and 3% of men had zolpidem concentrations that exceeded 50 ng/mL approximately 8 hours post-dosing. Also, it cannot be excluded that the risk of next morning driving impairment and somnambulism with the 5mg dose is lower as compared to the 10mg dose at population level.

Overall evidence in efficacy studies do not exclude that a 5 mg dose could be effective at individual level.

For individual patients, a lower dose of 5mg could be effective as stated in pharmacodynamic properties section of the SmPC and therefore in terms of benefit risk balance in individual patients the mention that 5 mg could be effective in some patients in posology section of the SmPC is recommended.

Isabelle Robine (FR)	6 March 2014	Signature: ……...