CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-997

OTHER REVIEWS

MEMORANDUM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: February 10, 2009

To: Russell Katz, M.D., Director
Division of Neurology Products

Through: Michael Klein, Ph.D., Director
Controlled Substance Staff

Silvia Calderon, Ph.D., Team Leader
Controlled Substance Staff

From: Alicja Lerner, MD, Ph.D., Medical Officer
Controlled Substance Staff

Subject: Abuse potential assessment of OX22 (Zolpidem tartrate) sublingual lozenges
Indication: Short term treatment of insomnia characterized by difficulties with sleep initiation
Dosage form and strengths: Sublingual lozenges (5 mg and 10 mg).
Submission: NDA 21-997 (5-16-2008) is located in the EDR.
Materials reviewed: Module 2: Section 2.5 Clinical Overview, section 2.5.2.6 -"Assessment of Abuse Potential"; Section 2.7.1- Summary of Biopharmaceutic Studies and Associated Analytical Methods; Module 3: Drug Product, section 3.2.P.2.2- Experiments to address FDA's request for potential abuse of zolpidem tartrate sublingual tablet; Module 5. Clinical Study Reports
NDA 21-997, 001 Amendment (6-13-2008), Module 1, section 1.14.1, Draft Labeling

Sponsor: Orexo, AB, SE-751 05 Uppsala, Sweden

- BACKGROUND

This memorandum summarizes key findings related to the CSS abuse potential assessment of OX22 (Zolpidem tartrate) sublingual lozenges in response to a consultation from the Division of Neurology Products.

Zolpidem tartrate is a nonbenzodiazepine hypnotic of the imidazopyridine class, which interacts with the gamma-aminobutyric acid (GABA) receptor. Numerous compounds, such as benzodiazepines and barbiturates, with central depressant effects potentiate the actions of GABA at the $GABA_A$ receptors. Zolpidem is listed in Schedule IV of the Controlled Substance Act (CSA).

Zolpidem tartrate immediate release tablets, 5 mg and 10 mg (Ambien, Sanofi-Aventis) are available since 1992 for short term treatment of insomnia. In 2005, Sanofi-Aventis marketed zolpidem tartrate controlled release tablets, 6.25 mg and 12 mg, (Ambien CR).

Orexo's primary objective for development of zolpidem tartrate sublingual tablet (OX-22) is to provide a more convenient, rapidly disintegrating tablet for sublingual administration which may provide an earlier onset of sleep than oral zolpidem, while maintaining a similar overall safety, efficacy, and abuse liability profile, for treatment of short-term insomnia in adult and geriatric populations.

Throughout development, three formulations were studied Formulation I, Formulation II and Final Commercial Product (FCP). A direct bioequivalence study comparing FCP to the commercially available 10-mg Ambien (zolpidem tartrate) tablet was not conducted. However, bioequivalence to Ambien was established by the bridging studies comparing the pharmacokinetic relationship between FCP, Formulation II and Ambien.

OX22 has been filed as a 505(b) (2) NDA submission utilizing Ambien as the reference listed drug.

The following sections summarize various aspects of the drug product that contribute to its abuse liability.

CONCLUSIONS AND RECOMMENDATIONS

1. CSS concurs that OX22 should remain subject to the controls imposed by Schedule IV of the CSA.
2. The studies to support a 505(b) (2) NDA submission were not designed to differentiate the abuse potential of OX-22 and Ambien.
3. The abuse potential of zolpidem as well as its amnestic effects[1] in conjunction with rapid dissolution of the tablets and the high solubility of zolpidem tartrate in

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[1] Anterograde amnesia is seen as an adverse effect of many sedative-hypnotics drugs including benzodiazepins and not-benzodiazepine hypnotic drugs such as zolpidem and zopiclone[1],[2],[4]. The mechanism of action seems to involve disruption of memory consolidation processes. Due to the fast onset of this action these drugs are known in the forensic medicine to be used to facilitate robbery and sexual-assaults in victims by giving them drinks containing these drugs[1]. Zolpidem related anterograde amnesia is partial or total and starts approximately 30 min after the drug administration and can be seen in up to 50% of patients at 45 min and in 40% patients at 60 min[3]. Zolpidem produces anterograde amnesia in dose-related fashion[4]. Zolpidem was also reported to produce somnambulism such as sleep driving, sleep cooking sleep, sleep shopping followed by amnesia to the event[5], this number reached 5.1% patients treated for insomnia in one retrospective study[6]. ([1] Goullé JP and Anger JP. Drug-facilitated robbery or sexual assault: problems associated with amnesia. Therapeutic Drug Monitoring. 2004; 26:206-210. [2] Canaday BR..Amnesia possibly associated with zolpidem administration. Pharmacotherapy 1996; 16(4):687-9. [3] Praplan-Pahud J, Forster A, Gamulin Z, Tassonyi E, Sauvanet J.-P. Preoperative sedation before regional anaesthesia. British Journal of Anaesthesia. 1990; 64:670-674. [4] Cashman J N, Power SJ, Jones RM. Assessment of a new hypnotic imidazo-pyridine (zolpidem) as oral premedication. British Journal of Clinical Pharmacology. 1987; 24:85-92. [5] Dolder CR, Nelson MH. Hypnosedative-induced complex behaviours: incidence, mechanisms and management. CNS Drugs 2008; 22(12):1021-1036. [6] Tsai JH, Yang P, Chen CC, Chung W, Tang TC, Wang SY, Liu JK. Zolpidem-induced amnesia and somnambulism: rare occurrences? European Neuropsychocopharmacology. 2009; (19):74-76.)

carbonated drinks, such as Coca Cola and beer, is of concern because it provides a means for the potential misuse of the product in commission of malicious criminal acts.

a. Thus, we request that the Sponsor propose strategies to minimize the potential abuse and misuse of the new formulation prior to approval.
b. In addition, the Sponsor should maintain active surveillance to capture abuse and misuse of the product and should report those cases to the Agency as expedited reports whether or not the case as a whole meets the regulatory requirements for a 15-Day Alert report.
c. The Sponsor should provide a list of MedDRA preferred terms that will capture all events of abuse and misuse of the formulation.
d. If, in fact, this new formulation is associated with higher levels of abuse and misuse, the Agency might have to consider the implementation of a Risk Evaluation and Mitigation Strategies (REMS) to maintain a positive benefit to risk ratio.

4. In the product label, pharmacokinetic parameters should be compared with those of Ambien.

I. CLINICAL PHARMACOKINETIC STUDIES

The Sponsor conducted four pharmacokinetic studies (OX22-001, OX22-004, OX22-005, OX22-008). Different formulations of OX22 lozenges 10 mg were compared in four studies in healthy volunteers to Ambien and to its European version, Stilnoct:
1) OX22-004, Formulation I versus Formulation II (10 mg OX22)
2) OX22-005, Formulation II (10 mg OX22) versus 10 mg Ambien
3) OX22-008, Formulation II versus FCP (10 mg OX22)
4) OX22-001, Formulation I versus 10 mg of the Stilnoct®, (oral zolpidem,Sanofi-Aventis , Europe)

Findings from OX22-005 study established that Formulation II was bioequivalent to Ambien tablets with respect to rate and extent of absorption. In study OX22-008, Formulation II was compared and found bioequivalent to FCP. In both studies, OX22-005 and OX22-008, the Sponsor reports that there were no statistically significant differences in T_{max}, C_{max}, AUC $_{0-t}$, and $AUC_{0-\infty}$

Central nervous system (CNS) active drugs with rapid onset of action are associated with **greater subjective effects that correlate with a drug's abuse potential as well as** psychomotor performance. It is known that the rate of onset and peak of a drug effect correlate with subjective and behavioral pharmacodynamic parameters. de Wit *et al.*[2] **have shown that higher measures on "euphoria" scales and greater** measurements of and longer lasting psychomotor impairment are produced by a single dose of diazepam than the same amount of diazepam dosed at intervals. Though both forms of administration

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[2] de Wit H, Dudish S, Ambre J. Subjective and behavioral effects of diazepam depend on its rate of onset. Psychopharmacology (1993), 112, 324-330)

produce similar peak plasma levels, an earlier T_{max} has been observed for the dose associated with higher liking and psychomotor impairment. [3, 4]

In the proposed product label, the Sponsor states that the FCP is ——— disintegrating sublingual tablet, which results in an earlier onset of absorption and a similar rate to that seen with zolpidem tartrate oral tablets. Following administration of a single 10 mg sublingual dose of the FCP in 36 healthy adult subjects (compiled data), the mean peak concentration (C_{max}) of zolpidem was 127 ng/mL (range: 52 to 277 ng/ml) occurring at a median time (T_{max}) of 101 minutes (range: 20-180). The mean AUC_{0-t} of zolpidem was 32048 ng*min/mL (range: 11754 to 83133 ng*min/mL). The label does not include pharmacokinetic parameters for Ambien for comparison purposes. b(4)

In general, data from studies OX22-005 and OX22-008 indicate that sublingually administered zolpidem was found to meet the regulatory criteria for bioequivalence to the commercially available oral tablet formulation when administered under fasting conditions. Although some possible but subtle differences between the two products with respect to their onset of action and absorption (T_{first} and C_{first}) were observed, these differences seem to be of no statistical significance and not to relate to the abuse potential of the new formulation.

II. CLINICAL PHARMACODYNAMIC STUDIES

The Sponsor performed two studies to evaluate the pharmacodynamic effects of OX22, one in healthy volunteers (OX22-002) and one in patients with insomnia (OX22-006).

The Sponsor evaluated the relationship between the pharmacokinetic profile and the sleep laboratory polysomnography/pharmacodynamic (PSG/PD) effects of 10 mg Formulation II and Ambien in the study OX22-006. The study OX22-006 was conducted with 70 primary chronic insomnia patients (18-64 years of age) to determine the hypnotic effect and safety of single 10 mg doses of OX22 Formulation II and Ambien 10 mg tablet. The study showed an earlier sleep onset of about 10 min for Formulation II, other sleep parameters were similar for both drugs. The Sponsor suggests that this difference might be due to the earlier absorption after administration of OX22 product as compared to Ambien and shown as shortened T_{first}.

The study OX22-002 compared 10 mg of the Stilnoct®, (oral zolpidem,Sanofi-Aventis , Europe) with 5 and 10 mg dosage form of OX22 Formulation I. This study conducted in healthy subjects (18-40 years of age), used a post-nap model and PSG, to determine the hypnotic effect and safety of single doses of 5 mg and 10 mg OX22 (Formulation I). The study showed 6 min earlier sleep onset for Formulation I as compared to Stilnoct.

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[3] Griffiths RR, McLeod DR, Bigelow GE, Liebson IA, Roache JD, Nowowieski P. Comparison of Diazepam and Oxazepam: Preference, Liking and Extent of Abuse. The Journal of Pharmacology and Experimental Therapeutics. 1984; 229 (2):501-8.

[4] De Witt H, Bodker B, Ambre J.. Rate of increase of plasma drug levels influences subjective response in humans. Psychopharmacology. 1991;107:352-8

Additionally, study OX22-007 was performed to evaluate the local tolerance and safety of sublingual zolpidem in insomnia patients. The study showed that sublingual zolpidem self-administered at a dose of 10 mg daily for 60 days did not cause any sublingual mucosal irritations, with the exception of a single episode of a single erythematous macule in one patient at one visit.

III- SOLUBILITY AND DETECTION OF OX22 ZOLPIDEM TARTATE SUBLINUAL LOZENGES IN COMMON BEVERAGES[5]

The Sponsor performed a number of studies to address FDA concerns regarding the abuse potential of zolpidem tartrate.

The first set of studies investigated the possibility of adding a dye to the OX22 formulation to prevent drug-related criminal activity. However, the Sponsor concluded that the addition of a dye to this formulation results in non-uniform color distribution. The addition of the color to the coating was also considered but the Sponsor felt that it could interfere with the desired disintegration and sublingual properties of the product. As part of the submission, the Sponsor provided pictures of the tablets to which a dye was added. These pictures showed that indeed the resulting tablets do not have a uniform color.

The next studies evaluated concentration, taste and appearance of sublingual zolpidem in common beverages in: water, ethanol (12%), beer, and Coca-Cola. These experiments were based on the suggested paper by Olsen et al.[6]

In the study examining the concentration of the drug in the common beverages one 10 mg sublingual tablet of zolpidem tartrate was placed into water, ethanol (12%), beer, and Coca-Cola without stirring, then 0.5 ml samples were taken and the amount of active substance was measured in each of the solvents.[7]The study showed that the drug would dissolve within the first 5 minutes in Coca-Cola and beer. At five minutes, the concentration of zolpidem tartrate in these drinks was determined to be 30 mg/L and 20 mg/L, respectively, which would correspond to 9.9 mg and 6.6 mg of zolpidem in the 330 ml drink.

The taste and appearance tests were performed by four persons. Two zolpidem tartrate sublingual tablets 10 mg were added to the four different beverages. The taste was measured with a score ranging from 0 – "no taste" to 5 – "extra strong taste", this test included taste of the spiked drink and "after taste" scores. The Sponsor did not provide individual data, instead the taste-scores from the four different subjects were added up and presented as a composite score results. In average values range from "1" for water

[5] EDR. NDA 21,977. Module 3, Section 3.2.P.2.2, Drug Product, Experiments to address FDA's request for potential abuse of zolpidem tartrate sublingual tablet.
[6] Olsen V, Gustavsen I, Bramness JG, Hasvold I, Karinen R, Asbjorg S, Christopherson J, Morland J. The concentrations, appearance and taste of nine sedating drugs dissolved in four different beverages. Forensic Science International. 2005;151:171-5
[7] EDR. NDA 21,977. Module 3, section 3.2.P.5.2, HPLC method MK 2197/Z 1462

which is coded "possible taste" up to "2.5" for ethanol which is "slight taste". The changes in the scores of "after taste" are somewhat higher in all beverages.

The changes in appearance of each beverage after 10 minutes of the addition of two tablets of the product were also reported. After the addition of two tablets to the Coca-Cola and beer, froth was observed, as well as sediment and particles were observed on the glass wall and floating in the beverage. However, these changes were observed 10 minutes after the addition of the tablets. Sediment and particles were also seen in water and ethanol. A "fat" surface was observed in Coke and water.

Nonetheless, the Sponsor concluded "that the appearance and taste of zolpidem tartrate sublingual tablets in water, ethanol (12%), beer, and Coca-Cola® indicated that there was a high possibility of detecting zolpidem tartrate, both due to its appearance and taste".

In conclusion it seems that the drug can be detected by individuals by a change of taste in all four beverages and by the aftertaste. However, these findings do not rule out the possibility that the tablets could be used to incapacitate a victim. By the time the victim realizes that the drink was spiked, he or she might already be experiencing the pharmacological effects of the drug.

IV. Overview of Adverse Events (AE) for FCP and Ambien [8]

The complete summary of adverse events for the system organ classes was performed using MedDRA Version 9.1. In this summary, adverse events from all clinical studies were pooled together and involved studies from OX-001 to OX-008, only the study OX-007 (with insomnia patients) and OX-008 (in healthy volunteers) used FCP, also only one study OX-007 used multiple dosing design. The comparison of AE's between FCP and Ambien shows that during treatment with FCP, 57.0% of subjects (N=79) experienced at least one adverse event as compared to 20.9% (N =19) treated with Ambien; in 40.5% of subjects treated with FCP the events were related, while in Ambien subjects 14.3% of AE's were considered related to the drug. The majority of AE's were seen in the class of Nervous System Disorders, Gastrointestinal (GI) Disorders, and Psychiatric Disorders during the treatment Comparisons of incidence of adverse events for FCP and Ambien are difficult because different study designs applied to each.

V- Abuse and Misuse of Zolpidem

The abuse potential of zolpidem has already been evaluated. The following subsections summarize data from the Drug Abuse Warning Network (DAWN) which contributed to the abuse evaluation of zolpidem as compared to other benzodiazepines, specifically by the number of abuse and misuse emergency department mentions.

- *Drug Abuse Warning Network (DAWN)*

[8] EDR. NDA 21,977. Module 5. Clinical Study Reports

DAWN is a public health surveillance system that monitors drug-related visits to hospital emergency departments (ED) and drug related deaths reported to DAWN by participating medical examiners and coroners (ME/Cs) to track the impact of drug use, misuse, and abuse in the U.S. The Substance Abuse and Mental Heath Administration (SAMHSA) is responsible for DAWN operations. DAWN relies on a national sample of general, non-Federal hospitals operating 24-hour EDs. The sample is national in scope, with oversampling of hospitals in selected metropolitan areas. In each participating hospital, ED medical records are reviewed retrospectively to find the ED visits that are related to recent drug use. All types of drugs- illegal drugs, prescription and over-the-counter (OTC) pharmaceuticals, dietary supplements, and nonpharmaceutical inhalants-are included. Alcohol, when it is the only drug implicated in a visit, is included for patients younger than age 21; alcohol, when it is present in combination with another drug, is included for patients of all ages.

DAWN not only captures ED visits associated with substance abuse/misuse, both intentional and accidental, but includes ED visits related to the use of drugs for legitimate therapeutic purposes.

Eight case types are defined in the new DAWN and each case is assigned into one and only one case type, the first that applies from the following hierarchy: "suicide attempt", "seeking detox", "alcohol only (age <21)", "adverse reaction", "overmedication", "malicious poisoning", "accidental ingestion", and "other."

DAWN Live! data 2003-2009, show that the majority of zolpidem related ED visits were associated with the use of higher doses of zolpidem than the prescribed or recommended doses, and with cases of abuse. Under DAWN, these visits are captured under the type of case defined as "Overmedication" and under the type of case identified as "Other", which captures ED visits associated with recreational use, drug abuse, drug dependence, withdrawal and misuse that can not be classified in any other way. Approximately 38 percent of the zolpidem related ED cases in 2003-2009 were identified as "Overmedication" cases, whereas 15 percent were classified as "Other". For the same period, approximately 23 percent of the cases were classified as "Suicide Attempt," 20 percent were classified as "Adverse Reactions," and 2 percent represented accidental ingestion.

As reported in DAWN, the nonmedical use of pharmaceuticals captures taking more than the prescribed dose of a prescription pharmaceutical or more than the recommended dose of an OTC pharmaceutical or supplement; taking a pharmaceutical prescribed for another individual; deliberate poisoning with a pharmaceutical by another person; and documented misuse or abuse of a prescription or OTC pharmaceutical or dietary supplement. Nonmedical use of pharmaceuticals may involve pharmaceuticals alone or pharmaceuticals in combination with illicit drugs or alcohol.

DAWN estimates that 536, 247 ED visits in 2004, 669,214 ED visits in 2005, 741,425 in 2006 and 855,838 in 2007 involved nonmedical use of prescription or OTC pharmaceuticals or dietary supplements.

Among the pharmaceuticals most frequently implicated in nonmedical use, benzodiazepines as a class increased 52 percent from 2004 to 2007, (from 143,546 to 218,640 estimated visits, respectively). As shown in **Table 1**, the number of estimated visits associated with the nonmedical use of zolpidem increased from 12,792 in 2004 to 18,464 in 2007. For comparison, increases were also reported from 2004 to 2007 of the numbers of estimated ED visits associated with the nonmedical use of benzodiazepines: alprazolam (46,526 ED visits in 2004 vs. 80,313 in 2007), diazepam (15,619 ED visits in 2004 vs. 19,674 in 2007), and lorazepam (17,674 ED visits in 2004 vs. 26,213 in 2007).

For the same period of time, the number of nonmedical ED visits associated with zolpidem rose 44 percent; 73 percent for alprazolam, 26 percent for diazepam and 48 percent for lorazepam. Although ED visits increased for all the benzodiazepines, it is important to note that the number of prescriptions sold for each drug product increased as well. In 2007, ——— prescriptions for zolpidem were dispensed in the United States ———, representing a ——— increase of the number of prescriptions dispensed from 2004. b(4)

In order to accommodate the differences in availability of each product, we calculated estimates of the nonmedical ED visits per 100,000 prescriptions sold ——— [9] As seen in **Table 1**, the rate for ED visits for zolpidem increased from 56 per 100,000 prescriptions sold in 2004 to 59 per 100,000 prescriptions sold in 2007. The rate of ED visits per 100,000 prescriptions sold for zolpidem in 2007 decreased when compared to the same rate calculated for zolpidem in 2006.

b(4)

The number of nonmedical zolpidem related ED visits in DAWN increased 44 percent from 2004 to 2007, whereas the number of dispensed prescriptions increased ——— for the same period of time. The number of nonmedical zolpidem related ED cases represent approximately 55 percent of the total zolpidem related cases captured in DAWN. The rate of nonmedical use ED mentions per 100, 000 prescriptions dispensed for zolpidem is lower than that of alprazolam, diazepam and lorazepam for 2004-2007.

9 ——— **measures retail** dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. The ——— **database integrates prescription activity** from a variety of sources including national retail chains, mass merchandisers, pharmacy benefits managers and their data systems, and provider groups.

Table 1: Calculated Rates of Nonmedical ED Visits in DAWN (2004-2007) per 100,000 Dispensed Prescriptions.

DRUGS	2004	2005	2006	2007
	DAWN TOTAL NONMEDICAL USE ED MENTIONS[1]			
Zolpidem	12,792	14,730	17,257	18,464
Alprazolam	46,526	57,419	65,236	80,313
Diazepam	15,619	18,433	19,936	19,674
Lorazepam	17,674	23,210	23,720	26,213
	PROJECTED PRESCRIPTIONS DISPENSED[2]			
Zolpidem				
Alprazolam				
Diazepam				
Lorazepam				
	RATES OF NONMEDICAL ED MENTIONS IN DAWN PER 100,000 PRESCRIPTIONS[3]			
Zolpidem	56	62	65	59
Alprazolam	135	161	168	189
Diazepam	125	145	150	141
Lorazepam	93	120	118	123

b(4)

[1] Source: SAMHSA, Office of Applied Studies, 2004-2006 DAWN-ED. Nonmedical use cases include the following type of cases: *Overmedication*, *Malicious Poisoning*, and *Other*; [2]

b(4)

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Maternal Health Team Label Review

Date: March 9, 2009 **Date Consulted:** March 3, 2009

From: Leyla Sahin, M.D.
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Through: Karen Feibus, MD
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To: Division of Neurology Products (DNP)

Drug: Zolpidem sublingual; NDA 21-997

Subject: Pregnancy and Nursing Mothers labeling

Materials Reviewed: Pregnancy and Nursing Mothers subsections of Zolpidem labeling.

Consult Question: Please review sections of the proposed label as they relate to pregnancy and lactation.

INTRODUCTION

On May 15, 2008, Orexo AB Sweden submitted a new drug application (NDA) 21 - 997 to the Division of Neurology Products (DNP) for zolpidem sublingual tablets. The sponsor's proposed

indication is for the short-term treatment of insomnia characterized by difficulties with sleep initiation.

On March 3, 2009, the DNP consulted the Maternal Health Team (MHT) to review the Pregnancy and Nursing Mothers section of the zolpidem package insert, and provide comment. This review provides revisions to the sponsor's proposed Pregnancy and Nursing Mothers subsections of zolpidem sublingual tablets' labeling.

BACKGROUND

The Maternal Health Team (MHT) is working to develop a more consistent and clinically useful approach to the Pregnancy and Nursing Mothers subsections of labeling. This approach complies with current regulations but incorporates "the spirit" of the Proposed Pregnancy and Lactation Labeling Rule (published on May 28, 2008).

As part of the labeling review, the MHT reviewer conducts a literature search to determine if relevant published pregnancy and lactation data are available that would add clinically useful information to the pregnancy and nursing mothers label subsections. In addition, the MHT presents available animal data, in the pregnancy subsection, in an organized, logical format that makes it as clinically relevant as possible for prescribers. This includes expressing animal data in terms of species exposed, timing and route of drug administration, dose expressed in terms of human dose equivalents (with the basis for calculation), and outcomes for dams and offspring. For nursing mothers, when animal data are available, only the presence or absence of drug in milk is considered relevant and presented in the label, not the amount.

This review provides revisions to the sponsor's proposed Pregnancy and Nursing Mothers subsections of zolpidem sublingual tablets' labeling.

SUMBMITTED MATERIAL

Sponsor's Proposed Pregnancy and Nursing Mothers Labeling

b(4)

b(4)

[redacted]

RECOMMENDATIONS

Provided below are the MHT's recommended revisions to the sponsors' proposed labeling. A track changes version of labeling that highlights all changes made was sent to the DNP by e-mail on March 9, 2009. Under "Highlights", the Maternal Health Team recommends qualifying the amount of infant exposure to prevent raising an inappropriate amount of concern, in view of the minimal amount of drug excreted into breast milk.

Highlights of Prescribing Information:

----------USE IN SPECIFIC POPULATIONS----------

Pregnancy: Based on animal data may cause fetal harm. Use only if clearly needed (8.1).
Nursing Mothers: Minimal infant exposure via breast milk (8.3).

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies in of TRADENAME in pregnant women. In animal reproduction and developmental toxicity studies, evidence of fetal harm was observed. TRADENAME should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Studies to assess the effects on children whose mothers took zolpidem during pregnancy have not been conducted. There is a published case report documenting the presence of zolpidem in human umbilical cord blood. Children born to mothers taking sedative-hypnotic drugs may be at some risk for withdrawal symptoms from the drug during the postnatal period. In addition, neonatal flaccidity has been reported in infants born of mothers who received sedative-hypnotic drugs during pregnancy.

Administration of zolpidem to pregnant rats and rabbits resulted in adverse effects on offspring development at doses greater than the maximum recommended human dose (MRHD) of 10 mg/day (8 mg/day zolpidem base); however, teratogenicity was not observed.

When zolpidem was administered at oral doses approximately 5, 24, and 120 times the MRHD (on a mg/m^2 basis) to pregnant rats during the period of organogenesis, dose-related decreases in fetal skull ossification occurred at all but the lowest dose. In rabbits treated during organogenesis with zolpidem at oral doses approximately 2.5, 10, and 40 times the MRHD (on a mg/m^2 basis), increased embryo-fetal death and incomplete fetal skeletal ossification occurred at the highest dose. The no-effect dose for embryo-fetal toxicity in rabbits is approximately 10 times the MRHD on a mg/m^2 basis. Administration of zolpidem to rats at oral doses approximately 5, 24, and 120 times the MRHD (on a mg/m^2 basis) during the latter part of pregnancy and throughout lactation produced decreased offspring growth and survival at all but the low dose.

8.3 Nursing Mothers

Zolpidem is excreted into human milk. Studies in lactating mothers indicate that the $t_{1/2}$ of zolpidem is similar to that in non-lactating women (2.6 ± 0.3 hours). Between 0.004% and 0.019 % of the total administered dose is excreted into milk. The effect of zolpidem on the nursing infant is not known. Caution should be exercised when TRADENAME is administered to a nursing mother.

CONCLUSIONS

While the Proposed Pregnancy and Lactation Labeling Rule, published May 2008, is in the clearance process, the MHT is structuring the Pregnancy and Nursing Mothers label information in a way that is in the spirit of the Proposed Rule while still complying with current regulations.

The goal of this restructuring is to make the pregnancy and lactation sections of labeling a more effective communication tool for clinicians.

The MHT's recommended labeling for zolpidem sublingual tablets is provided on pages 3-4 of this review.