NATIONAL PBM COMMUNICATION · January 16, 2013

Zolpidem and FDA-Proposed Lower Doses Due To Impaired Mental Alertness

- FDA mandates making label changes to lower doses of immediate and extended-release zolpidem products (Ambien®, Ambien CR®, Edluar®, Zolpimist®) at bedtime due to impaired mental alertness the following morning. New dosing recommendations do not apply to Intermezzo®, a lower dose zolpidem product approved for middle-of–the-night awakenings.
    - Pharmacokinetic and driving simulation studies show that blood levels of zolpidem above 50ng/mL may cause impairment while operating a vehicle and increase the risk of accidents.
        - Extended-release formulations impart greater next-morning impairment than immediate-release formulations.
        - Women are more susceptible to next-morning impairment due to a slower rate of elimination for zolpidem than men.
    - Studies have detected blood levels of zolpidem over 50ng/mL as much as 8 hours post-dose.
        - Trials involving 10 mg Ambien (or bioequivalent zolpidem products) resulted in 15% of women and 3% of men with zolpidem concentrations that exceeded 50 ng/mL approximately 8 hours post-dosing.
        - Trials of zolpidem extended-release 12.5 mg resulted in approximately 33% of women and 25% of men with zolpidem blood concentrations exceeding 50 ng/mL approximately 8 hours post-dosing.
- FDA requires that manufacturers of affected zolpidem products revise product labeling to reflect lower recommended doses and to warn that higher than recommended doses may more likely impair activities requiring full alertness the next morning, including driving.

PRODUCT	CURRENT DOSING IN PRODUCT LABEL	NEW DOSING RECOMMENDED BY FDA
Ambien, Edluar, Zolpimist (and generic equivalents)	Men and Women: 10 mg once daily, immediately before bedtime	Women: 5 mg once daily, immediately before bedtime Men: 5 or 10 mg once daily, immediately before bedtime
Ambien CR (and generic equivanlent)	Men and Women: 12.5 mg once daily, immediately before bedtime	Women: 6.25 mg once daily, immediately before bedtime Men: 6.25 or 12.5 mg once daily, immediately before bedtime

- FDA recommends that healthcare practitioners should:
    - Prescribe the lowest dose capable of treating patients' insomnia symptoms;
    - Caution patients regarding possible impairment in driving and activities that require alertness the next morning, ***despite feeling fully awake***.
- VA MedSAFE recommends that providers should:
    - Consider inquiring about morning driving and other morning activities in patients who take zolpidem or similar medications.
    - Consider discontinuing the medication or lowering the dose if patients feel drowsy in mornings after using sleeping medications such as zolpidem.
    - Notify patients to watch for morning drowsiness and for any signs of impaired driving (or other activities) when taking any sleeping medication.
    - Continue to report any adverse reactions with the use of any zolpidem product(s) or other drugs for the treatment of insomnia by entering the information into CPRS' Allergies/Adverse Reactions field and/or via local reporting mechanisms. Adverse events should also be reported, as appropriate, to the VA ADERS program and FDA MedWatch (1-800-FDA-1088, fax 1-800-FDA-0178, online at https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm, or by mail).
- The Zolpidem Immediate Release Recommendation for Use text within the Primary Care Outpatient Algorithm: Treatment of Acute and Chronic Insomnia document is in the process of being updated. Providers/staff are encouraged to become familiar with other areas within the document that provides additional information/resources regarding the management of insomnia including a basic sleep history, sleep hygiene education, and other modalites such as Cognitive Behavioral Therapy (CBT).

REFERENCES

FDA Drug Safety Communication: Risk of next-morning impairment after use of insomnia drugs; FDA requires lower recommended doses for certain drugs containing zolpidem (Ambien, Ambien CR, Edluar, and Zolpimist). http://www.fda.gov/Drugs/DrugSafety/ucm334033.htm . (Accessed 01/11/13).

ACTIONS:

- ***Facility Director*** *(or physician designee): Forward this document to the Facility Chief of Staff (COS).*
- ***Facility COS and Chief Nurse Executives:*** *Forward this document to all appropriate providers who prescribe this agent (e.g.,* ***primary care providers, including contract providers***, etc.*). In addition, forward to the Associate Chief of Staff (ACOS) for Research and Development (R&D). Forward to other VA employees as deemed appropriate.*
- ***ACOS for R&D:*** *Forward this document to Principal Investigators (PIs) who have authority to practice at the facility and to your respective Institutional Review Board (IRB).*