

## INTERMEZZO

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Hi. This is Danielle MacDonald, clinical pharmacist with the Lakewalk and Proctor locations. I am going to speak to you today about Intermezzo, which is essentially a new formulation of an existing medication, zolpidem tartrate, but in a different formulation, like I mentioned. It was approved by the FDA on November 23 and is manufactured by Transcept Pharmaceuticals.

The name choice was no mistake. For those of you that are musically inclined, Intermezzo is by definition a composition which fits in between other musical entities -- thus, the place in therapy between pieces of sleep, so for those individuals who wake up in the middle of the night, earlier than they would anticipate. It is a non-benzodiazepine sedative hypnotic, as you know, from the brand name that has been available for a number of years. It does interact with the GABA-BZ complex much like benzodiazepines do; however, it is preferential for the alpha subunit and so exhibits essentially sedative effects. It is relatively devoid of the mild relaxant and anticonvulsant effects of benzodiazepines that achieve that activity through nonselective binding to that complex.

As mentioned, just last week the FDA approved for the first time for this condition the use of Intermezzo as needed for the treatment of insomnia when middle of the night awakening is followed by difficulty returning to sleep. One big limitation of use, and this is going to be an important educational point for patients, is that they do need to ensure they have four hours of dedicated time for sleep after using the product, and that kind of came out of a safety issue noted when 40 healthy individuals attempted to drive after using the product in fewer than four hours and their function was impaired.

The FDA is requesting some additional data from Transcept to ensure that patients are very clear on the dosing so, of course, the four-hour deadline that they need to commit to, and also to ensure that they are not waking up, taking the product, and then waking up later and risking an overdose of taking another pill, so they have devised it in a unit dose pouch and there are some very clear recommendations on the medication guide for how they should place it at their bedtime stand and by their clock.

Intermezzo was evaluated in two randomized double-blind, placebo-controlled trials. A total of about 400 patients were studied, and both objective and subjective evaluation of their sleep, time to fall back to sleep, was statistically significantly improved and that was evidenced by patient report, as well as polysomnography.

The dosing information for Intermezzo is dependent on gender. It is recommended that men use a 3.5 mg dose while women use half of that, the 1.75 mg dose. As you know,

this is approximately one-quarter to one-third of the dose of the active drug that is currently available for the zolpidem oral tablets, but it is available as a sublingual tablet.

The theory is that placing it under the tongue would allow for quicker onset of action and also increased clearance so decreased duration of action. Patients should not swallow the tablet whole, and the manufacturer identified that the reason women should use a lower dose is that they found that women are clearing the drug less quickly than men, which is kind of curious. Some caveats – they do recommend decreasing the dose to that of 1.75 mg if the patient is also using other CNS depressants because there can be additive effects in the geriatric population, most notably in those older than 70 years, as there was increased confusion and oversedation which, of course, led to their increased risk of falls. It does need to be adjusted in hepatic impairment. However, no dosage adjustment is necessary for those with renal impairment at this time.

The absorption of Intermezzo is greatly affected by food and it is recommended to avoid snacking, so those of you that turn to your Ben & Jerry's in the middle of the night, please try to abstain. In fact, the effect of absorption was delayed by two to three times potentially and the duration, which is of more concern for patients who might have that hangover effect that could impair their driving function.

At this point in time, given its new approval, the only known contraindication is in patients who have exhibited hypersensitivity to the zolpidem itself. There are some precautions, again like I mentioned, for those that are using CNS depressants. There can be additive effects including the use of benzodiazepines, opioids, and tricyclic antidepressants, as well as alcohol, so patients are encouraged to not use the product if they have used alcohol that evening or even 24 hours prior to sleep. Certainly, ensure that evaluation of comorbid diagnoses are being looked into, especially if insomnia does not remit after seven to ten days of treatment. Much like Ambien, there is evidence of complex behaviors, sleep-driving, decreased inhibition, and so forth, in patients that have used the product, and even some amnesia, not recalling that they are exhibiting those behaviors.

Another caution in those with depression, make sure you are monitoring them for any worsening mood or suicidal thoughts, and also a caution for those even with mild to moderate sleep apnea.

Common side effects of Intermezzo include headache, nausea, and fatigue at the incidences that you see on the slide, 5 percent, 4 percent and 3 percent.

As you can see on the slide, there are some links to more information on this drug. I'm sure more information will be coming out as we see how the drug is affected in patient populations as they start to use it. As you know, zolpidem has been available as a generic oral tablet since the patent expired last year. It is already among one of the shortest-acting of the sleep aids available and has been marketed as the next extended release product Ambien CR for those with sleep maintenance concerns. Patients in practice have actually taken half of a dose of a 5 or 10 mg oral tablet (of course, that's off label), and the effect

of duration of the oral tablets is typically three to four hours for a lot of patients but certainly can be longer, so this sublingual dose offers the possibility of a quicker onset of action and a shorter duration. I really see it as a potential for patients to use the product for treatment, so in the middle of the night, versus prophylactically using it before they fall asleep in anticipation that they might wake up, so I can certainly see some utility there.

There is no word yet on cost or formulary coverage of the agent but it likely will be more costly than the available sleep options, especially since Ambien is available generically and, of course, it does not replace the need in somebody who has sleep concerns to educate them regarding appropriate sleep hygiene.

Thank you for watching this Essentia Health Med Moment video.