FDA Approves Melatonin Agonist for Insomnia

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The Food and Drug Administration has approved an insomnia drug with a unique mechanism of action and several features unique among hypnotics approved for insomnia: It is not a controlled substance and does not produce some CNS side effects associated with other hypnotics approved for insomnia, according to one of the drug's investigators.

The drug, ramelteon, a melatonin receptor agonist, was approved in July for treating insomnia characterized by difficulty with sleep onset. Ramelteon binds to melatonin MT_1 and MT_2 receptors, two of the three known melatonin receptors. It is believed to be effective in potentiating sleep, since the receptors "acted upon by endogenous melatonin, are thought to be involved in the maintenance of the circadian rhythm underlying the normal sleep-wake cycle," according to the drug's label.

Ramelteon, which will be marketed as Rozerem by Takeda Pharmaceuticals Inc., will not be available until late September, the company said in a statement. In two studies of patients with chronic insomnia—one in people aged 18-64 and another in those aged 65 and older—those taking ramelteon fell asleep faster and slept longer than those on placebo. The recommended dosage is 8 mg taken within 30 minutes of going to bed; it should not be taken with or immediately after a high-fat meal.

In an interview with this newspaper, Gary Richardson, M.D., senior research scientist at the Sleep Research Center at Henry Ford Hospital, Detroit, said ramelteon does not produce the CNS sedation, memory impairment, or imbalance that are side effects of the other hypnotic drugs approved for insomnia, the benzodiazepines and the newer nonbenzodiazepines—a particular advantage in elderly patients. Because the action of the drugs is specific to the M_1 and M_2 receptors, which are located only in the suprachiasmatic nuclei (SCN), the activity of the drug is specific.

There are precautions and potential drug interactions to consider, however: Ramelteon should not be used in people with severe hepatic impairment and should be used cautiously in those with moderate hepatic impairment. CYP1A2 is the major isoenzyme involved in metabolizing ramelteon, so it cannot be taken with fluvoxamine, a strong CYP1A2 inhibitor, and should be administered with caution with drugs that are weaker CYP1A2 inhibitors, according to the drug's label. Other drugs on a list of drugs that may have effects on ramelteon metabolism include rifampin, a strong CYP enzyme inducer. Cautious use with strong CYP3A4 inhibitors, such as ketoconazole, and strong CYP2C9 inhibitors, such as fluconazole, are among the other recommendations.

Ramelteon does not produce central nervous system sedation, memory impairment, or imbalance seen with hypnotics approved for treating insomnia.

Another consideration is that increases in serum prolactin have been documented in some women and men on ramelteon, with no clinical effects. But the label advises that prolactin and testosterone levels should be considered in patients with unexplained amenorrhea, galactorrhea, reduced libido, or problems with fertility. Dr. Richardson, an investigator in trials and a consultant to Takeda, said that although the increases in prolactin levels in women were self-limited and below what an endocrinologist would consider pathological, this finding should be kept in mind, particularly because some women may have unrecognized mild to moderate hyperprolactinemia at baseline and may be more susceptible to this potential effect.

Melatonin, taken as a supplement, has never been shown to be effective as a hypnotic taken at bedtime to promote sleep. This may be related to a metabolite of melatonin, which increases with increasing doses and prevents it from being effective, he said. Ramelteon is not scheduled as a controlled substance. In a study evaluating its abuse potential in 14 people with a history of sedative/hypnotic abuse or anxiolytic abuse, no differences were found between a placebo and increasing doses of ramelteon. ■

References: 1. Data on file. Pfizer Inc., New York, NY. **2.** Keck PE, Versiani M, Potkin S, West SA, Giller E, Ice K, and the Ziprasidone in Mania Study Group. Ziprasidone in the treatment of acute bipolar mania: a three-week, placebo-controlled, double-blind, randomized trial. *Am J Psychiatry.* 2003;160:741-748.