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 last month for treating insomnia characterized by difficulty with sleep onset. Ramelteon binds to melatonin MT1 and MT2 receptors, two of the three known melatonin receptors. This action may potentiate 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—both in elderly patients. Because the action of the drug is specific to the MT1 and MT2 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 en-

zyme inducer.

Cautious use with strong CYP3A4 inhibitors, such as ketoconazole, and strong CYP2C9 inhibitors, such as fluconazole, are among the other recommendations. 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.

As a supplement, melatonin has never been shown to be an effective hypnotic when taken 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, there were no differences between a placebo and increasing doses of ramelteon.