NEW DRUG - Ramelteon (*Rozerem*™)

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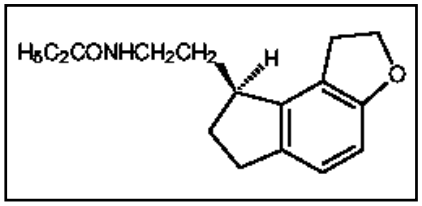
Ramelteon was approved by the Food and Drug Administration in July 2005 as an orally active hypnotic for the treatment of transient and chronic insomnia in adults. Ramelteon, developed by Takeda Global Research and Development Center, has the first novel mechanism of action developed in 35 years in the field of sleep research. It is the first and only non-scheduled prescription sleep medication. Unlike other sleep agents, ramelteon shows no GABA or opiate receptor affinity. Its mechanism of action is that of a melatonin MT_1 and MT_2 receptor agonist. These receptors are located in the suprachiasmatic nuclei in the brain, which regulate the body's sleep-wake cycle. Recommended dosage is 8 mg. Rozerem™ is distributed by Takeda Pharmaceuticals as a round, pale orange-yellow, film-coated, 8 mg tablets, with "TAK" and "RAM-8" printed on one side.

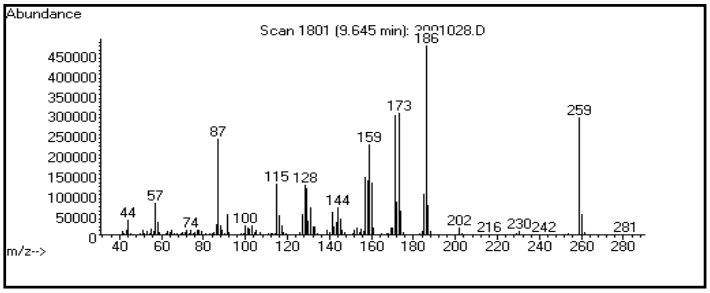
Pharmacokinetics

Ramelteon reaches a peak plasma concentration in 0.5 to 1.5 hours (mean = 0.75) and has a volume of distribution of 73.6 L. Ramelteon is 70% protein bound to albumin. It undergoes oxidative metabolism to hydroxyl and carbonyl derivatives catalyzed primarily by CYP1A2 followed by glucuronidation, with minor involvement by CYP2C subfamily and CYP3A4. Ramelteon undergoes rapid, high first pass metabolism. This is supported by data indicating individuals taking ramelteon show substantial C_{max} and AUC variability with approximately 100% coefficient of variability. Less than 0.1% of the initial dose is excreted in the urine and feces combined as parent compound with 84% urinary recovery and 4% fecal recovery of radiolabeled ramelteon. Elimination was almost complete by 96 hours post-dose with no significant accumulation due to the short half-life of elimination of 1 to 2.6 hours. The major metabolite of ramelteon is M-II. M-II is active with one-tenth and one-fifth the binding affinity of the parent molecule for the MT_1 and MT_2 receptors, respectively. The metabolite circulates at a greater concentration than the parent compound, producing a 20-100 fold greater mean systemic exposure. The elimination half-life of M-II is 2 to 5 hours, independent of dose.

Chemistry

Ramelteon has a formula weight of 259.34 ($C_{16}H_{21}NO_2$). It is freely soluble in methanol, ethanol, and dimethyl sulfoxide. It is only slightly soluble in water and aqueous buffers pH 3 to 11. A crushed pill standard was prepared from the medical evidence and utilized to determine analytical properties. Ramelteon extracted via a basic liquid/liquid extraction with an acid back extraction and was easily detected on both the GC/MS and GC/NPD. IUPAC name: (S)-N-[2-(1,6,7,8-tetrahydro-2H-indeno-[5,4-b]furan-8-yl)ethyl]propionamide.





Relative elution order: Bupivacaine, Benztropine, **ROZEREM**, Norsertraline, Sertraline
m/z ions: 186, 259, 171, 57, 115, 128

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