A Continuous-Release Ion-Powered Pump Melatonin Delivery System that Overcomes Challenges of Release and Absorption in the Intestines

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Introduction

Several modified release formulations of melatonin have been developed with the goal of providing exogenous melatonin profiles that mimic normal endogenous levels, i.e., Mesa Wave-shaped plasma pharmacokinetic profile for sleep maintenance. There have been difficulties in overcoming the challenges of release and absorption of melatonin in the higher pH environments in the small and large intestines. The initial attempts at employing hydroxypropylmethylcellulose (HPMC) to provide sustained-release and absorption showed that there was a problem in maintaining high plasma melatonin levels after the first 4 hours after administration. Various approaches, including adding a controlled-release coating to melatonin beads, administering immediate-release and controlled-release melatonin tablets simultaneously, using melatonin soft gels instead of powder, and slow-release pills of melatonin suspended in an 80:20 mixture of peanut oil/beeswax, have been tried. Further improvements in these delivery systems are needed to get closer to the body’s own Mesa Wave-shaped profile (Figure 1A-D). The patented Ion Powered Pump (IPP) delivery system utilized in continuous-release and absorption melatonin (CRA-melatonin) was developed to overcome the challenges of release and absorption in the intestines.

Figure 1. Melatonin Plasma Concentration Time Profiles for Modified-Release Formulations of Melatonin

- A Coated Beads
- B Bilayer Tablet

Methods

• The melatonin was formulated in a polymer matrix that maintains a solubility-enhancing and concentration gradient driven low pH environment (Ion Powered Pump). This facilitates the continuous release and absorption of melatonin in the GI tract, independent of local pH conditions.
• The active ingredient in CRA-melatonin (Ultramel) is an ultra pure (99%) proprietary synthetic melatonin.
• Randomized, crossover clinical PK evaluation comparing 5 mg CRA-melatonin (REMfresh) with the market-leading 5 mg immediate-release melatonin (IR-melatonin) in 10 healthy non-smoking adults.
• Blood was taken pre-dose and at 0.25, 0.5, 0.75, 1, 2, 3, 4, 5, 6, 8, and 12 hours following administration and was assayed for melatonin by a validated LC-MS/MS method.
• Pharmacokinetic (PK) parameters, including the time course, Cmax, Tmax, and plateau time for melatonin were determined by inspection.

Results

- Serum melatonin concentrations measured 0-24 h after 0.4 mg or 4 mg of melatonin. For both doses, immediate-release (25% of the total dose) and controlled-release (75% of the total dose) melatonin tablets were simultaneously administered to create a surge-sustained release effect.

CRA-melatonin was designed as a hydrogel matrix tablet. There is rapid release of the hydrogel from the surface of the tablet, as the hydrogel release controlling matrix is setting up in the acidic environment (pH of 1 to 3.5) in the stomach. As the tablet moves into the higher pH (5.5 to 6.5) environment of the small intestine, which is above the pKa of melatonin (~4.0), the acidic moiety in the tablet maintains the pH within the tablet below 4.0 for 7+ hours. The hydrogel matrix, after proper hydration, allows continuous release of the active melatonin and acidic moiety into the lumen of the intestines. This proprietary approach facilitates delivery of the active melatonin to the brush border of the epithelial layers of the small and large intestines for uptake into the bloodstream.

Figure 3. Median Concentrations of Plasma Melatonin after 5 mg CRA-melatonin

- Median concentrations of plasma melatonin 0-12 h after 5 mg of CRA-melatonin. The CRA-melatonin delivery technology allowed burst release and absorption of approximately 50% of the melatonin within the first 3 hours, helping facilitate sleep onset, coupled with sustained-release and absorption of approximately 50% of the remaining melatonin within the next 4 hours, to optimize sleep maintenance.

Conclusions

• The patented CRA-melatonin provides a burst release for rapid absorption above threshold levels and maintains successful melatonin release and absorption to address the historical challenges with exogenous melatonin delivery.
• CRA-melatonin provides the desired PK profile, anticipated to result in faster onset of sleep and then helping with sleep maintenance for up to 7 hours.

References


DISCLOSURES
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The hazard ratio represents an individual’s relative risk of dying compared with the general population.1,2 Chronic disorders of sleep and wakefulness affect an estimated 50 to 70 million Americans, and long-term sleep deprivation has been associated with a number of negative health consequences, including an increased risk of diabetes, hypertension, heart attack, stroke, obesity, and depression.1 Currently available immediate-release melatonin (IR-melatonin) formulations help promote sleep onset, but their non-sustained absorption in the lower gastrointestinal tract makes it more difficult for them to enable adequate sleep maintenance. Sleep maintenance for an optimal duration is becoming even more relevant, since shorter sleep duration is associated with greater mortality as shown in Figure 1.1,2

Introduction

Chronic disorders of sleep and wakefulness affect an estimated 50 to 70 million Americans, and long-term sleep deprivation has been associated with a number of negative health consequences, including an increased risk of diabetes, hypertension, heart attack, stroke, obesity, and depression.1 Currently available immediate-release melatonin (IR-melatonin) formulations help promote sleep onset, but their non-sustained absorption in the lower gastrointestinal tract makes it more difficult for them to enable adequate sleep maintenance. Sleep maintenance for an optimal duration is becoming even more relevant, since shorter sleep duration is associated with greater mortality as shown in Figure 1.1,2

Figure 1. Shorter Sleep Duration is Associated with Greater Mortality

The hazard ratio represents an individual’s relative risk of dying compared with the general population.1,2 The patented Ion Powered Pump (IPP) delivery system utilized in the continuous-release and absorption melatonin (CRA-melatonin) was developed to provide an exogenous melatonin pharmacokinetic (PK) profile that mimics normal endogenous melatonin plasma level patterns through a novel technology. The REM Absorption Kinetics Trial (REMAKT) evaluated the PK profile of CRA-melatonin compared with a leading marketed IR-melatonin formulation. REMAKT had a 1000 pg/mL target of plasma melatonin concentration for sleep maintenance. This target was set at about 10 times the endogenous peak concentration for melatonin found in healthy young subjects,2 since studies of drug transport across the blood-brain barrier have shown that there is an approximately 10-fold lower concentration of exogenous melatonin in the brain versus plasma.3

Methods

- Randomized, crossover clinical PK evaluation comparing 5 mg CRA-melatonin (REMfresh) with the market-leading 5 mg IR-melatonin in 10 healthy non-smoking adults
- The active ingredient in CRA-melatonin (Ultramel) is an ultra pure (99%) proprietary synthetic melatonin
- Blood was taken pre-dose and at 0.25, 0.5, 0.75, 1, 2, 3, 4, 5, 6, 8, and 12 hours following administration and was assayed for melatonin by a validated LC-MS/MS method
- PK parameters, including the time course, Cmax, and Tmax for melatonin were determined
- Time to reach initial target (1000 pg/mL) and duration of time above the target threshold levels for melatonin were determined by interpolation
- Assessment of adverse events was adjudicated by the Medical Monitor, Dr. Lassiter

Results

Figure 2. Median Concentrations of Plasma Melatonin after 5 mg CRA-melatonin or 5 mg IR-melatonin

The median Cmax was 4,690 pg/mL for CRA-melatonin and 23,352 pg/mL for the IR-melatonin. Melatonin levels exceeded the target sleep maintenance threshold level of 1000 pg/mL for a median of 6.7 hours for CRA-melatonin, compared to 3.7 hours for IR-melatonin.

Table 1. Subjects Reporting TreatmentEmergent Adverse Events

<table>
<thead>
<tr>
<th>Subject/Product/Date Administered</th>
<th>All Verbatim</th>
<th>Onset</th>
<th>Duration</th>
<th>Related</th>
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<td>006/IR-melatonin/Mar 16</td>
<td>Irritability</td>
<td>29-Mar-16</td>
<td>4 h</td>
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<td>Nausea</td>
<td>16-Apr-16</td>
<td>1 min</td>
<td>Possible</td>
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<tr>
<td>009/IR-melatonin/Apr 16</td>
<td>Emesis</td>
<td>13-Apr-16</td>
<td>3 days</td>
<td>Possible</td>
</tr>
<tr>
<td>009/IR-melatonin/Apr 16</td>
<td>Stomach Cramps</td>
<td>13-Apr-16</td>
<td>3 days</td>
<td>Possible</td>
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<tr>
<td>009/IR-melatonin/Apr 16</td>
<td>Emesis</td>
<td>16-Apr-16</td>
<td>1 min</td>
<td>Possible</td>
</tr>
</tbody>
</table>

Five treatment-emergent adverse events (TEAEs) occurred with IR-melatonin. There were no TEAEs associated with CRA-melatonin.

Conclusions

- The market leading IR-melatonin formulation spiked 23X higher than the targeted levels of exogenous melatonin for sleep maintenance
- IR-melatonin also had a rapid decline in serum levels that did not allow melatonin levels to be maintained beyond 4 hours above the targeted maintenance threshold
- CRA-melatonin, a patented novel melatonin formulation, was shown to achieve both quick release of melatonin to induce sleep, and then continuous release and absorption of melatonin to help maintain sleep over 7 hours, by remaining above the targeted maintenance threshold

References


DISCLOSURES

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Melatonin levels decline with age, an important factor in poor quality sleep among older people. In addition to difficulty falling asleep, sleep in older populations is characterized by increased fragmentation of the sleep architecture and sleep maintenance problems. Melatonin supplementation has been shown to promote and maintain sleep in older populations. Previously, prolonged-release melatonin (PR-M), which has been marketed internationally, was designed to provide a serum melatonin profile more closely related to the normal physiological release pattern compared with immediate-release melatonin (IR-melatonin).

A pharmacokinetic study looking at serum melatonin levels in healthy males after ingestion of the 2 mg dose of PR-M shows peak concentration of melatonin in the blood occurring at 2.6 hours and persisting over 3.5 hours after ingestion and declining towards the morning. IR-melatonin peaks after 2 hours and rapidly declines over the next 2 hours.

In well-conducted sleep studies, PR-M demonstrated statistically significant improvements in sleep quality, morning alertness, and quality of life in patients aged 55 years and older compared with IR-melatonin and placebo. In addition, as shown in Table 1, the responder rate for concomitant improvement in quality of sleep and morning alertness, and in each of them separately, was significantly higher for PR-M compared with placebo, in studies reported by the PR-M innovator.

**Table 1. % Responders to PR-M vs Placebo Showing Concomitant and Clinically Meaningful Improvement in Quality of Sleep and Morning Alertness**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>QOS &amp; BFW Responders</th>
<th>QOS Responders</th>
<th>BFW Responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR-M</td>
<td>32.4%</td>
<td>18.7%</td>
<td>48%</td>
</tr>
<tr>
<td>Placebo</td>
<td>18.7%</td>
<td>48%</td>
<td>18.7%</td>
</tr>
</tbody>
</table>

**Figure 2. Median Concentrations of Plasma Melatonin after 5 mg CRA-melatonin**

The median it took plasma melatonin levels to exceed the initial threshold level of 1000 pg/mL was 0.42 hours for CRA-melatonin. The median C_{max} was 4,690 pg/mL for CRA-melatonin, and the median time to reach this concentration (T_{max}) was 1.5 hours. Melatonin levels showed a median plateau time of 6.7 hours with CRA-melatonin. There were no treatment-emergent adverse events seen with CRA-melatonin.

**Conclusions**

- CRA-melatonin shows an enhancement over the already advanced profile of PR-M. There was a faster time to C_{max}, a median plateau time extending to 6.7 hours and rapid fall-off in plasma levels.
- The faster time to C_{max} is anticipated to result in improved sleep onset.
- The extended plateau time and rapid fall-off at the end of the Mesa Wave is anticipated to improve sleep maintenance and morning alertness.

**References**