

Melatonin

5 mg

Sublingual Tablets



Product Summary:

Sublingual melatonin is used to improve the quality of sleep in those with an age-related decline in melatonin. Sublingual melatonin is also used to reestablish a normal circadian sleep rhythm in those suffering from disturbed sleep patterns relating to jet lag, shift-work, and in delayed sleep phase syndrome (DSPS).

Properties/Uses:

The claim as approved by the *Natural Health Products Directorate* (NHPD): Helps increase total sleep time (aspect of sleep quality) in people suffering from sleep restriction or altered sleep schedule (e.g., shift-work and jet lag). Helps reduce the time it takes to fall asleep in people with delayed sleep phase syndrome and reset the sleep-wake cycle of circadian rhythm.



NERVOUS



Pharmacology:

Melatonin is a *neurohormone* made in the pineal gland of the brain. It plays a facilitating role in achieving the *sleep-phase* of the inborn 24-hour *sleep-wake rhythm* or cycle, also called the *circadian rhythm*. The workings of the 24-hour sleep-wake cycle is embedded in and regulated by approximately 10,000 brain cells called the *biological clock*, or *bio-clock*. The bio-clock is able to keep track of time over 24 hours, knowing when the *sleep-phase* of the cycle should be imposed.

Melatonin *facilitates* sleep by acting as a natural sedative that effectively tones down the brain's activating system that mediates wakefulness. However, sleep is not just the absence of wakefulness. Sleep is a positive neurologically imposed program that proceeds successfully when wakefulness is inhibited by melatonin's sedation. Healthy sleep cannot be achieved if activated wakefulness does not subside. Insomnia can be thought of as a condition in which wakefulness overrides the brain's effort to impose sleepiness. Normally, melatonin levels rise in the bloodstream as light diminishes progressively to full darkness. By approximately 10:00 PM, melatonin blood levels can be high enough in most people to support effective sedation for the onset of sleep, if a person commits to sleeping by going to bed in a dark room.

Melatonin is thought to act in at least two ways in relation to maintaining a restful sleep pattern. Firstly, melatonin is known to produce a sedative effect in animals and humans. This sedative effect is thought to stem from enhanced gammaaminobenzoic acid (GABA) receptor binding, producing an inhibitory action on the reticular activating system, which mediates wakefulness.¹⁻³ Melatonin is necessary to turn-down imposed wakefulness, but such sedation is not sufficient for the establishment of sleep. Sleep like wakefulness is imposed, but by another set of neurological properties mediated by the SCN circadian clock governing the sleep-wake rhythm. A rising melatonin plasma level commensurate with room darkness facilitates the onset of sedation, and this presumably matches a mounting SCN clock commitment to impose sleep.

The second way melatonin acts to ensure a restful sleep pattern pertains to SCN clock synchronization. As the seasonal dark-light pattern varies throughout the year, the SCN clock must adapt to the way sleep requirements change in real time. Endogenous melatonin is thought to act as an entrainment agent to accomplish this adaptation.^{4,5,6} Entrainment is the complex process of re-synchronizing the biological clock with real time. Critical incremental changes in dim light timing, serve as entrainment information for re-setting the clock. The SCN neurons are able to decipher the trending darkness pattern, mirrored in the corresponding dark-mediated melatonin plasma levels. SCN neurons continuously perceive shifts in melatonin as a function of the dark-light cycle, adapting the clock imposed sleep-wake rhythm throughout the year accordingly.

Desynchronization is a condition of failed adaptation and is represented in the concept of a phase-shift. In other words, the sleep-phase of the sleep-wake circadian rhythm has been shifted to another time that is out of synch with real time.





Usually the sleep-phase is pushed or shifted forward, meaning sleep is postponed or delayed. The overt use of exogenous melatonin can induce entrainment to correct for desynchronization^{5,7,8} Such entrainment may provide completely satisfactory management of jet-lag, shift work, or more challenging sleep aberrations as seen in DSPS, depression, or Alzheimer's disease. In more challenging categories, physician or pharmacist guidance may be more appropriate than selfmedication alone. Melatonin can entrain the free-running circadian rhythms of blind people and it has been used to treat the symptoms of circadian maladaptation associated with delayed sleep-phase syndrome.^{6,7,8}

Who May Benefit from Sublingual Melatonin Use?

The most likely candidate for trying sublingual melatonin is the older person who appears to have an age-related decline in adequate melatonin secretion, evidenced by frequent or chronic insomnia. Frequent insomnia can cause problems during the day, such as sleepiness, fatigue, difficulty in concentrating, and irritability, as well as other subtle health problems. Taking sublingual melatonin at bedtime is expected to be beneficial in this category of people. Shift workers may also find melatonin helpful to adjust to new sleep patterns when changing shifts. For jet-lag, taking melatonin may help travelers achieve a regular sleep pattern more quickly in their new time zone than waiting for the body to adjust naturally. Using melatonin in sublingual tablet form is preferable because it is absorbed more efficiently into the bloodstream than when taken orally and absorbed through the stomach.





Manufactured product information:

Manufacturer:

WN Pharmaceuticals® Ltd.

Size/UPC:

100s7 77747 10300 3

NPN:

80008343

Expiry Date:

48 months from date of manufacture

Active Ingredient:

Each tablet contains:

Melatonin 5 mg

Non-Medicinal Ingredients (in descending order):

Lactose monohydrate, microcrystalline cellulose, peppermint flavour, croscarmellose sodium, magnesium stearate.

Appearance:

White, round, bisected tablet with peppermint odour.

Packaging:

175 cc white round bottle with safety seal under a 38 mm white induction sealed cap with vented interior seal and a label applied to the bottle. Lot number and expiry date are printed on label applied to exterior of bottle.

Storage:

Store in tightly sealed container in a cool, dry place.





Dose:

The NHPD Monograph for Melatonin indicates 0.1 to 10 mg once a day at bedtime.

Directions:

(Adults): Adults only. At bedtime only, allow to dissolve under the tongue, 1–2 tablets once daily or as recommended by a physician. For use beyond 4 weeks, consult a physician.

Caution:

The caution as approved by the *Natural Health Products Directorate* (NHPD):

KEEP OUT OF THE REACH OF CHILDREN. Consult a physician prior to use if you have a hormonal disorder, diabetes, liver or kidney disease, cerebral palsy, seizure disorders, migraine, depression and/or hypertension, or if you are taking blood pressure or sedative/hypnotic medications. If symptoms persist continuously for more than 4 weeks (chronic insomnia), consult your physician. Do not drive or use machinery for 5 hours after taking melatonin. Do not use if you are taking immunosuppressive drugs and/or if you are pregnant or breastfeeding. STORE AT ROOM TEMPERARTURE IN A DARK, DRY PLACE. DO NOT USE IF SEAL UNDER CAP IS BROKEN OR MISSING.



Driving Performance:

The impact of melatonin use on driving performance remains a central concern. One published investigation was conducted by the University of Zurich Travel Clinic, in the Institute of Social and Preventative Medicine.⁹ Researchers investigated the effects of melatonin on driving performance parameters in 20 men and women aged 21-57 years.

On each testing day, subjects received 5 mg or placebo, taken at 4:30 PM. One hour later, a test series was performed consisting of a medical examination, body sway measurement, and a standardized driving computer test battery to assess attention, reaction time, power of concentration, and sensomotor coordination. Subjective sleepiness was measured on three occasions during each test session using the Stanford Sleepiness Scale questionnaire.

Results: In assessing the results, the investigators reported that only one of the 16 main variables of the driving computer test battery [selective attention tested by signal-detection] was significantly affected by melatonin. However, even those values were still within normal range. Subjective sleepiness was increased by melatonin, although this affect became significant only after the prolonged concentration task. Neither the medical examination nor the body sway test demonstrated signs of drug influence.

Conclusion: The researchers concluded that overall the results of the computer test battery demonstrated no objective adverse impact of melatonin on driving performance. However, due to the increased subjective sleepiness after administration of melatonin, caution should be exercised when driving under the influence of melatonin.

The administration of melatonin is usually well tolerated, but it can be associated with mild adverse effects.

Dollins et. al. using higher than normal doses of 10, 20, 40 or 80 mg in 20 healthy males found that all doses compared to placebo significantly decreased oral temperature, the number of correct responses in auditory vigilance, response latency in reaction time, and selfreported vigor.¹⁴

Other reports include headache, transient depressive symptoms, fatigue, confusion, drowsiness, mild tremor, mild anxiety, dizziness, and abdominal cramps.^{11, 14-17}

Dagan et. al. found in a six-week treatment course with 61 DSPS patients, using 5 mg at 10pm, that 57.4 percent reported no adverse effects, 34.4 percent reported slight daytime fatigue, and 8.2 percent reported headaches and nausea.⁷

Melatonin, its analogs, and its metabolites are not mutagenic, and melatonin possesses remarkably low acute toxicity in animals and humans.¹⁸





Deficiency Symptoms:

Individuals may experience reduced quality of sleep.

Drug Interactions/Contraindications:

The contraindications to appear on the label as approved by the NHPD: Consult a physician prior to use if you have a hormonal disorder, diabetes, liver or kidney disease, cerebral palsy, seizure disorders, migraine, depression and/or hypertension or if you are taking blood pressure or sedative/hypnotic medications. Do not use if you are taking immunosuppressive drugs and/or if pregnant or breastfeeding.

Melatonin may interact adversely when used in combination with medications for improving sleep. One study found a combination of melatonin and zolpidem had reports of nausea, vomiting, amnesia, and somnambulism (sleep-walking) to the point of incapacitation.¹⁰

Melatonin may potentiate the anticoagulant and antiplatelet actions of medications or herbs used to modulate blood clotting.¹¹

Melatonin may have the ability in diabetic patients to impair glucose utilization and increase insulin resistance.¹¹

Because contraceptive drugs can elevate endogenous melatonin, concomitant use of melatonin could be associated with melatonin adverse effects.¹¹

Flumazenil may inhibit the effect of melatonin.¹¹

Fluvoxamine significantly inhibits the elimination of melatonin.¹² In one study, a 17-fold higher ($P < .05$) area under the concentration-time curve and a 12-fold higher ($P < .01$) serum peak concentration of melatonin was found.¹²

Melatonin can decrease the effectiveness of Nifedipine GITS monotherapy in the modulation of blood pressure.¹³ Lusardi et. al. found in a placebo-controlled, double-blind, and cross-over study with 47 well controlled mild to moderate hypertensive patients on 30-60 mg daily of Nifedipine GITS, that when 5 mg of melatonin was added nightly over 4 weeks, there was a daily average increase in systolic blood pressure of 6.5 mmHg and in diastolic blood pressure of 4.9 mmHg, with an average increase in heart rate of 3.9 beats per minute. The DBP and HR were particularly evident during the morning and the afternoon hours.





Allergen Content/Ingredient Sensitivity:

NO	YES
Artificial Colors	Corn Products
Artificial Flavors	Milk Products
Artificial Sweeteners	Starch/Modified Starch
Egg Products	
Fish	
Gluten	
Hydrolyzed Plant Protein	
Lecithin	
Peanuts	
Preservatives	
Sesame Products	
Shellfish	
Soy Products	
Sulphites	
Tartrazine	
Tree Nuts	
Wheat Products	
Yeast	

NOT ACCEPTABLE FOR THE FOLLOWING DIETARY RESTRICTIONS:

Free of animal products

Kosher





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