Melatonin 10 mg Dual-Action Caplets

Product Summary:

The inability to fall asleep or obtain enough sleep because of travelling or shift-work can be stressful and have a negative impact on the following day. Once the cycle of irregular sleep patterns begins, it is hard to stop. Melatonin is a natural hormone that helps regulate the sleep-wake cycle. By resetting this cycle, melatonin can improve your length of sleep and quality of sleep. This bi-layer caplet releases one half of the melatonin right away to put you to sleep and the other half is a timed release to keep you dozing.

Properties/Uses:

The claim approved by *Natural Health Products Directorate* (NHPD): Helps increase the 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 relieve the daytime fatigue associated with jet lag. Helps reduce the time it takes to fall asleep in people with delayed sleep phase syndrome and reset the body's sleep-wake cycle (aspect of the circadian rhythm).

NERVOUS

Pharmacology:

Melatonin is a neurohormone produced in the pineal gland located in the center of the brain and is associated with inducing a sedative effect. Melatonin's primary roles are the regulation of the body's circadian rhythm, endocrine secretions and sleep patterns. Melatonin helps resynchronize the cycles of patients suffering from insomnia related to jet lag, shift work and other neuropsychiatric disorders such as depression and autism.[1] It is also helpful for circadian rythym sleep disorders in blind children and adults. Melatonin seems to be involved in a variety of other physiological processes, such as seasonal reproductive cycles, cancer development and growth, immune activity, and antioxidation.[2]

Exogenous melatonin results in a rapid, transient, mild sleep-inducing effect. Melatonin supplements can shift the body's circadian rhythm. Supplementation can also lower body temperature and blood pressure, as well as reduce alertness and performance for up to 4 hours after oral administration. Melatonin is also helpful in reducing the frequency of cluster headaches, presumably by lowering body temperature. Furthermore, melatonin is a powerful antioxidant with 6-10 times the activity as vitamin E.[2]

Melatonin & Sleep Disorders:

During conditions of dim light, special retinal photoreceptors spontaneously release norepinephrine, activating neural pathways that run to the pineal gland, through the suprachiasmatic nuclei (SCN) in the hypothalamus. This results in pineal synthesis of melatonin and its passive diffusive secretion into the bloodstream.[3] Most aspects of physiology and behavior are time-integrated by sensitive biological clock mechanisms centered in the suprachiasmatic nuclei (SCN) of the hypothalamus, which acts on neural and endocrine pathways to regulate a variety of different circadian rhythms so that internal states vary predictably over a 24-hour cycle.[4]

With hypothalamic SCN sleep regulation, most people achieve a satisfactory sleep-wake circadian rhythm over each 24- hour day. However, due to age-related decline in endogenous melatonin synthesis, jet travel over time zones, or shift work, a discrepancy can arise between the established biological "sense" of time, and the actual local time. Such desynchronization causes the biological clock to impose a sleep-wake rhythm that is out of synch with local time, resulting in sleep deficits and numerous minor physiological and psychological complaints.[5] A condition of chronic desynchronization that typically requires clinical management is delayed sleep-phase syndrome (DSPS).

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.[6-8] 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.[9-11] 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.[10-13] 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 self medication 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.[11-13]

Dagan *et al.* described the results of a 6-week clinical trial for treating 61 DSPS patients using 5 mg of melatonin.[12] A survey of the patients was conducted between 12 and 18 months after the 6-week melatonin treatment ended. Dagan and his fellow investigators stated that their findings confirm earlier evidence that melatonin was effective in changing the sleep-wake patterns of DSPS patients. However, they also found that the new sleep patterns were not permanently retained; suggesting that exogenous melatonin does not cause a fundamental and permanent change in sleep regulation, thus DSPS patients may need to take melatonin regularly.[12]

Lewy and fellow investigators generated a phase-response curve (PRC) to melatonin that demonstrated circadian phase advances with melatonin administration in the late afternoon and evening, and circadian phase delays with administration in the later hours of sleep and the morning.[13] Their observations offer some basis on how to empirically time a melatonin dose in DSPS, but also in better managing sleep problems associated with shift work and on going episodes of jet lag.

A recently published double-blind, placebo-controlled, randomized crossover trial was conducted on 86 shift-work nurses with insomnia disorders. They took 5 mg of melatonin about 30 minutes before night time sleep and had significantly decreased sleep onset latency and increased sleep quality as compared with placebo.[14]

Recent research has been investigating the use of melatonin as an anti-cancer agent, down the reproduction of cancerous cells, as well as a cancer-fighting agent that promotes cancer cell death when taken during cancer treatment. One meta-analysis reported that there was a substantial reduction in risk of death with low adverse events reported.[15] A recent meta-analysis found that the use of melatonin alongside tradional therapy for cancer led to substantial improvements in tumor remission, 1-year survival, and alleviation of radiochemotherapy-related side effect.[16]

Manufacturer product information:

Manufacturer:
WN Pharmaceuticals® Ltd.

Size/UPC:
60's 7 77747 10301 0

NPN:
80040522

Expiry Date:
24 months from date of manufacture

Active Ingredient:
Each caplet contains:

Melatonin ..... 10 mg

Non-Medicinal Ingredients (in descending order):
Microcrystalline cellulose, dibasic calcium phosphate dihydrate, carbohydrate gum, magnesium stearate, sodium copper chlorophyllin, croscarmellose sodium.

Appearance:
White and green bilayer oval caplet.

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 the label applied to the exterior of the bottle.

Storage:
Store in a well closed container in a cool, dry place.

Dose:

As per the NHPD Monograph for sublingual melatonin, the adult dose is 0.1-10 mg once per day at or before bedtime.[17]

Safe and effective use of melatonin for non-sleep disorders, such as cancer, have been seen in dosages greater than 10 mg.[1] One study on the toxicology of chronic melatonin found the daily consumption of 10 mg of melatonin over a one month period to be safe.[18]

The sublingual route compared to the oral route is expected to provide a more consistent bioavailability of melatonin. Early pharmacokinetic studies indicated that 30 to 60 percent of an oral dose is metabolized during the first pass in the liver.[19] Furthermore, absorption of melatonin via the gut is thought to be highly variable.[9]

For prevention of cluster headache, an evening dose of 10 mg has been used.[2]

Melatonin in Children:

Since melatonin is an endogenous human neurohormone, its use in children is expected to be safe, and effective on an empirical basis in children suffering from sleep problems associated with a variety of reasons.[20-24] In most cases of childhood chronic insomnia, a physician should be consulted for guidance in melatonin dosing and administration timing.

A recent review of melatonin treatment of sleep disorders in children with intellectual disabilities concluded that a wide range of doses of melatonin are used in children, but most of the trials with a positive result used a dose of 2.5 mg and above.[25] Another review of melatonin treatment in children with neurodevelopmental disabilities showed that the dose of melatonin used in these children ranged from 2 to 10 mg. None of the doses was associated with significant adverse effects.[26]

Directions:

(Adults): 1 caplet daily at or before bedtime, or as recommended by a physician. For use beyond 4 weeks, consult a physician.

Caution:

The caution approved by *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 hyper tension, or if you are taking blood pressure or sedative/hypnotic medications. Do not drive or use machinery for 5 hours after taking melatonin. If symptoms persist continuously for more than 4 weeks (chronic insomnia), consult a physician. Do not use if you are taking immunosuppressive drugs and/or if you are pregnant or breastfeeding. STORE AT ROOM TEMPERATURE IN A DARK, DRY PLACE. DO NOT USE IF SEAL UNDER CAP IS BROKEN OR MISSING.

Deficiency Symptoms:

Melatonin production can be abnormally low in certain conditions or disease states. For example, insomniacs typically have low levels of melatonin.[2]

Drug Interactions/Contraindications:

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 somnambulia (sleep-walking) to the point of incapacitation.[27]

Melatonin may potentiate the anticoagulant and antiplatelet actions of medications or herbs used to modulate blood clotting.[28]

Melatonin may have the ability in diabetic patients to impair glucose utilization and increase insulin resistance.[28]

Because contraceptive drugs can elevate endogenous melatonin, concomitant use of melatonin could be associated with melatonin adverse effects.[28]

Flumazenil may inhibit the effect of melatonin.[28]

Fluvoxamine significantly inhibits the elimination of melatonin. 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.[29]

Melatonin can decrease the effectiveness of Nifedipine GITS monotherapy in the modulation of blood pressure. 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.[30]

Melatonin can stimulate immune function and might interfere with immunosuppressive therapy. Do not use with immunosuppresant drugs.

Do not use in people with seizure disorder. Dopamine is considered an endogenous down-regulator of seizure activity and melatonin is capable of causing a decrease in dopamine output within areas of the brain thought to participate in the control of epileptic seizure.[31]

Toxicity/Adverse Reactions:

Melatonin may cause daytime drowsiness. However, the frequency of this side-effect is the same as that with a placebo.[2]

The administration of melatonin is usually well tolerated, but it can be associated with mild adverse effects. Reports include headache, transient depressive symptoms, fatigue, confusion, drowsiness, mild tremor, mild anxiety, dizziness, and abdominal cramps.[2] Rare allergic symptoms have been to occur, as well as mild gastrointestinal symptoms.[17]

Dagan et. al. found in a six-week treatment course with 61 DSPS patients, using 5 mg at 10 pm, that 57.4 percent reported no adverse effects, 34.4 percent reported slight daytime fatigue, and 8.2 percent reported headaches and nausea.[12]

Melatonin, its analogs, and its metabolites are not mutagenic, and melatonin possesses remarkably low acute toxicity in animals and humans.[32]

Allergen Content/Ingredient Sensitivity:

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

ACCEPTABLE FOR THE FOLLOWING DIETARY RESTRICTION:

Free of animal products

NOT ACCEPTABLE FOR THE FOLLOWING DIETARY RESTRICTION:

Kosher

References:

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