

## MELATONIN

- Date:** December 7, 2006
- Proper name(s):** Melatonin (Sweetman 2002) or N-acetyl-5-methoxytryptamine (Buscemi *et al.* 2004)
- Common name(s):** Melatonin, Pineal hormone (O'Neil 2001)
- Source material(s):** Synthetic (requires citation of an approved NHP Master File, authorized by a letter of access issued to the applicant by the NHP Master File's registered owner)
- Pineal gland of non-human animals (Buscemi *et al.* 2004) other than those susceptible to Transmissible Spongiform Encephalopathy (TSE) diseases including Bovine Spongiform Encephalopathy (BSE) (NHPD LC IAS 2006)
- Route(s) of administration:** Oral or sublingual (Buscemi *et al.* 2004)
- Dosage form(s):** Those suited to the allowable route(s) of administration.
- Use(s) or Purpose(s):** Statement(s) to the effect of:
- ▶ 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 (Buscemi *et al.* 2004; Zhdanova *et al.* 2001; Shamir *et al.* 2000; Skene *et al.* 1999; Brusco *et al.* 1999; Sanders *et al.* 1999; Dolberg *et al.* 1998; Suhner *et al.* 1998b; Garfinkel *et al.* 1995; Haimov *et al.* 1995; Petrie *et al.* 1993; Claustrat *et al.* 1992; Sack *et al.* 1991; Petrie *et al.* 1989).
  - ▶ Helps relieve the daytime fatigue associated with jet lag (Buscemi *et al.* 2004).
  - ▶ Helps to reduce the time it takes to fall asleep (sleep onset latency aspect of sleep quality) in people with delayed sleep phase syndrome (Buscemi *et al.* 2004).
  - ▶ Helps re-set the body's sleep-wake cycle (aspect of the circadian

rhythm) (Buscemi *et al.* 2004, Kunz *et al.* 2004, Sack *et al.* 2000).

**Dose(s):**

Subpopulation: Adults only (IOM 2004)

Quantity:

- ▶ 0.1-10 mg 1 time per day, at or before bedtime (Brzezinski *et al.* 2005; IOM 2004; Andrade *et al.* 2001; Kayumov *et al.* 2001; Koda-Kimble 2001; Smits *et al.* 2001; Zhdanova *et al.* 2001; Citera *et al.* 2000; Shamir *et al.* 2000; Brusco *et al.* 1999; Jean-Louis *et al.* 1999; Matsumoto 1999; Dolberg *et al.* 1998; Lewy *et al.* 1998; Suhner *et al.* 1998a; Attenburrow *et al.* 1996; Garfinkel 1995; Haimov *et al.* 1995; Tzischinsky and Lavie 1994; Dollins *et al.* 1993; Dahlitz *et al.* 1991; James *et al.* 1987)

**Duration of use:**

For use beyond 4 weeks, consult a health care practitioner (Buscemi *et al.* 2004; IOM 2004).

**Risk information:**

Statements to the effect of:

Cautions and warnings: Consult a health care practitioner 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 (IOM 2004; Ninomiya *et al.* 2001; Cagnacci *et al.* 2001; Lusardi *et al.* 2000; Carman *et al.* 1976).

If symptoms persist continuously for more than 4 weeks (chronic insomnia), consult your health care practitioner (Dipiro *et al.* 2002).

Contraindications: Do not use if you are taking immunosuppressive drugs (Lissoni *et al.* 1999).

Do not drive or use machinery for 5 hours after taking melatonin (Avery *et al.* 1998).

Do not use if you are pregnant or breastfeeding (IOM 2004).

**Non-medicinal ingredients:** Must be chosen from the current NHPD List of Acceptable Non-Medicinal Ingredients and must meet the limitations outlined in the list.

**Specifications:** Must comply with the minimum specifications outlined in the current NHPD Compendium of Monographs.

**References:**

Andrade C, Srihari BS, Reddy KP, Chandramma L. Melatonin in medically ill patients with insomnia: a double blind placebo-controlled study. *Journal of Clinical Psychiatry* 2001;62(1):41-5.

Attenburrow ME, Cowen PJ, Sharpley AL. Low dose melatonin improves sleep in healthy middle-aged subjects. *Psychopharmacology (Berlin)* 1996;126(2):179-81.

Avery D, Lenz M, Landis C. Guidelines for prescribing melatonin. *Annals of Medicine* 1998;30(1):122-30.

Brusco LI, Fainstein I, Marquez M, Cardinali DP. Effect of melatonin in selected populations of sleep-disturbed patients. *Biological Signals and Receptors* 1999;8(1-2):126-31.

Brzezinski A, Vangel MG, Wurtman RJ, Norrie G, Zhdanova I, Ben-Shushan A, Ford I. Effects of exogenous melatonin on sleep: a meta-analysis. *Sleep Medicine Reviews* 2005;9:41-50.

Buscemi N, Vandermeer B, Pandya R, Hooton N, Tjosvold L, Hartling L, Baker G, Vohra S, Klassen T. Melatonin for treatment of sleep disorders. Evidence Report/Technology Assessment No. 108. AHRQ Publication No. 05-E002-2. Rockville (MD): U.S. Department of Health and Human Services, Agency for Healthcare Research and Quality. November, 2004.

Cagnacci A, Arangino S, Renzi A, Paoletti AM, Melis GB, Cagnacci P, Volpe A. Influence of melatonin administration on glucose tolerance and insulin sensitivity of postmenopausal women. *Clinical Endocrinology (Oxford)* 2001;54(3):339-46.

Carman JS, Post RM, Buswell R, Goodwin FK. Negative effects of melatonin on depression. *American Journal of Psychiatry* 1976;133(10):1181-1186.

Citera G, Arias MA, Maldonado-Cocco JA, Lazaro MA, Rosemffet MG, Brusco LI, Scheines EJ, Cardinalli DP. The effect of melatonin in patients with fibromyalgia: a pilot study. *Clinical Rheumatology* 2000;19(1):9-13.

Claustrat B, Brun J, David M, Sassolas G, Chazot G. Melatonin and jet lag: confirmatory result using a simplified protocol. *Biological Psychiatry* 1992;32(8):705-11.

Dahlitz M, Alvarez B, Vignau J, English J, Arendt J, Parkes JD. Delayed sleep phase syndrome response to melatonin. *Lancet* 1991;337(8750):1121-4.

DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM. *Pharmacotherapy: A Pathophysiological Approach*. 5th edition. New York (NY): McGraw-Hill Co. Inc.; 2002.

Dolberg OT, Hirschmann S, Grunhaus L. Melatonin for the treatment of sleep disturbances in major depressive disorder. *American Journal of Psychiatry* 1998;155(8):1119-21.

Dollins AB, Lynch HJ, Wurtman RJ, Deng MH, Lieberman HR. Effects of illumination on human nocturnal serum melatonin levels and performance. *Physiology and Behavior* 1993;53(1):153-60.

Garfinkel D, Laudon M, Nof D, Zisapel N. Improvement of sleep quality in elderly people by controlled-release melatonin. *Lancet* 1995;346(8974):541-4.

Haimov I, Lavie P, Laudon M, Herer P, Vigder C, Zisapel N. Melatonin replacement therapy of elderly insomniacs. *Sleep* 1995;18(7):598-603.

IOM 2004: Institute of Medicine Committee on the Framework for Evaluating the Safety of Dietary Supplements. Prototype monograph on melatonin. *Dietary Supplement Ingredient Prototype Monographs, Developed as Examples for the Report Dietary Supplements: A Framework for Evaluating Safety*. Institute of Medicine and the National Research Council of the National Academies, Washington (DC): National Academies Press 2004: D1-D71.

James SP, Mendelson WB, Sack DA, Rosenthal NE, Wehr TA. The effect of melatonin on normal sleep. *Neuropsychopharmacology* 1987;1(1):41-4.

Jean-Louis G, von Gizycki H, Zizi F. Predictors of subjective sleepiness induced by melatonin administration. *Journal of Psychosomatic Research* 1999;47(4):355-8.

Kayumov L, Brown G, Jindal R, Buttoo K, Shapiro CM. A randomized, double-blind, placebo-controlled crossover study of the effect of exogenous melatonin on delayed sleep phase syndrome. *Psychosomatic Medicine* 2001;63(1):40-8.

Koda-Kimble MA, editor. *Applied Therapeutics: The Clinical Use of Drugs*. Baltimore (MD): Lippincott Williams and Wilkins; 2001.

Kunz D, Mahlberg R, Müller C, Tilmann A, Bes F. Melatonin in patients with reduced REM sleep duration: two randomized controlled trials. *Journal of Clinical Endocrinology & Metabolism* 2004;89(1):128-134.

Lewy AJ, Bauer VK, Cutler NL, Sack RL. Melatonin treatment of winter depression: a pilot study. *Psychiatry Research* 1998;77(1):57-61.

Lissoni P, Barni S, Mandala M, Ardizzoia A, Paolorossi F, Vaghi M, Longarini R, Malugani F, Tancini G. Decreased toxicity and increased efficacy of cancer chemotherapy using the pineal hormone melatonin in metastatic solid tumor patients with poor clinical status. *European Journal of Cancer* 1999;35:1688-92.

Lusardi P, Piazza E, Fogari R. Cardiovascular effects of melatonin in hypertensive patients well controlled by nifedipine: a 24-hour study. *British Journal of Clinical Pharmacology* 2000;49:423-7.

Matsumoto M. The hypnotic effects of melatonin treatment on diurnal sleep in humans. *Psychiatry and Clinical Neurosciences* 1999;53(2):243-5.

Ninomiya T, Iwatani N, Tomoda A, Miike T. Effects of exogenous melatonin on pituitary hormones in humans. *Clinical Physiology* 2001 May;21(3):292-9.

NHPD LC IAS 2006: Natural Health Products Directorate Leadership Committee Issue Analysis Summary, May 15, 2006.

O'Neil MJ, editor. *The Merck Index: An Encyclopedia of Chemicals, Drugs and Biologicals*. 13th ed. Whitehouse Station (NJ): Merck & Co. Inc; 2001.

Petrie K, Dawson AG, Thompson L, Brook R. A double-blind trial of melatonin as a treatment for jet lag in international cabin crew. *Biological Psychiatry* 1993;33(7): 526-30.

Petrie K, Conaglen JV, Thompson L, Chamberlain K. Effect of melatonin on jet lag after long haul flights. *British Medical Journal* 1989;298(6675):705-7.

Sack RL, Brandes RW, Kendall AR, Lewy AJ. Entrainment of free-running circadian rhythms by melatonin in blind people. *New England Journal of Medicine* 2000;343 (15):1070-7.

Sack RL, Lewy AJ, Blood ML, Stevenson J, Keith LD. Melatonin administration to blind people: phase advances and entrainment. *Journal of Biological Rhythms* 1991;6(3):249-61.

Sanders DC, Chaturvedi AK, Hordinsky JR. Melatonin: aeromedical, toxicopharmacological, and analytical aspects. *Journal of Analytical Toxicology* 1999;23(3):159-67.

Shamir E, Laudon M, Barak Y, Anis Y, Rotenberg V, Elizur A, Zisapel N. Melatonin improves sleep quality of patients with chronic schizophrenia. *Journal of Clinical Psychiatry* 2000;61(5):373-7.

Skene DJ, Lockley SW, Arendt J. Melatonin in circadian sleep disorders in the blind. *Biological Signals and Receptors* 1999;8(1-2):90-5.

Smits MG, Nagtegaal EE, van der Heijden J, Coenen AM, Kerkhof GA. Melatonin for chronic sleep onset insomnia in children: a randomized placebo-controlled trial. *Journal of Child Neurology* 2001;16(2):86-92.

Suhner A, Schlagenhauf P, Johnson R, Tschopp A, Steffen R. Comparative study to determine the optimal melatonin dosage form for the alleviation of jet lag. *Chronobiology International* 1998a;15(6):655-6.

Suhner A, Schlagenhauf P, Tschopp A, Hauri-Bionda R, Friedrich-Koch A, Steffen R. Impact of melatonin on driving performance. *Journal of Travel Medicine* 1998b;5(1):7-13.

Sweetman SC, editor. *Martindale: The complete drug reference*. 33<sup>rd</sup> edition. London (UK): Pharmaceutical Press; 2002.

Tzischinsky O, Lavie P. Melatonin possesses time-dependent hypnotic effects. *Sleep* 1994;17(7):638-45.

Zhdanova IV, Wurtman RJ, Regan MM, Taylor JA, Shi JP, Leclair OU. Melatonin treatment for age-related insomnia. *Journal of Clinical Endocrinology and Metabolism* 2001;86(10):4727-30.