MELATONIN - ORAL

For Melatonin products with a sublingual route of administration, please use the Melatonin-sublingual monograph.

This monograph is intended to serve as a guide to industry for the preparation of Product Licence Applications (PLAs) and labels for natural health product market authorization. It is not intended to be a comprehensive review of the medicinal ingredient.

Notes

- Text in parentheses is additional optional information which can be included on the PLA and product label at the applicant’s discretion.
- The solidus (/) indicates that the terms and/or the statements are synonymous. Either term or statement may be selected by the applicant.

Date

May 13, 2013

Proper name(s)

- N-[2-(5-Methoxy-1H-indol-3-yl)ethyl]acetamide (Martindale 2012; Merck 2012)
- N-Acetyl-5-methoxytryptamine (Martindale 2012; Merck 2012)

Common name(s)

Melatonin (Merck 2012; Buscemi et al. 2004)

Source material(s)

Melatonin (Merck 2012)

Route(s) of administration

oral (Buscemi et al. 2004)

Dosage form(s)

- The acceptable pharmaceutical dosage forms include, but are not limited to capsules, chewables (e.g. gummies, tablets), liquids, powders, strips or tablets.
- This monograph is not intended to include foods or food-like dosage forms such as bars, chewing gums or beverages.
Use(s) or Purpose(s) Statement(s) to the effect of

- Helps to increase the total sleep time (aspect of sleep quality) in people suffering from sleep restriction or altered sleep schedule (e.g. shift-work, jet lag) (Zhdanova et al. 2001; Shamir et al. 2000; Skene et al. 1999; Brusco et al. 1999; Sanders et al. 1999; Dolberg et al. 1998; Garfinkel et al. 1995; Haimov et al. 1995; Sack et al. 1991).

- Helps to prevent and/or reduce the effects of jet lag (e.g. daytime fatigue, sleep disturbance) for people travelling by plane easterly across two or more time zones (Brown et al. 2009; Herxheimer and Petrie 2009; Suhner et al. 1998a; Petrie et al. 1993; Clausrat et al. 1992; Petrie et al. 1989).

- Helps to reduce the time it takes to fall asleep (sleep onset latency aspect of sleep quality) in people with delayed sleep phase disorder (van Geijlswijk et al. 2010).

- Helps to re-set the body’s sleep-wake cycle (aspect of the circadian rhythm) (van Geijlswijk et al. 2010; Kunz et al. 2004; Sack et al. 2000).

Dose(s) Statement(s) to the effect of

Subpopulation(s)
adults (≥ 19 years) (IOM 2004)

Quantity(ies)

All uses except jet lag:

Jet lag:
0.5-10 mg, per day (Brown et al. 2009; Herxheimer and Petrie 2009; Suhner et al. 1998a)

Directions for use

All uses:
Do not drive or use machinery for 5 hours after taking melatonin (Avery et al. 1998; Suhner et al. 1998b).

All uses except jet lag:
2001).

Jet lag:
Take once a day at bedtime after darkness has fallen, while travelling, and at destination until adaptation to the new daily pattern (Brown et al. 2009; Herxheimer and Petrie 2009).

See Appendix 1 for examples of dosage preparations, frequencies of use and directions for use, according to cited references. The purpose of Appendix 1 is to provide guidance to industry.

**Duration of use**

Statement(s) to the effect of

All uses except jet lag:
For use beyond 4 weeks, consult a health care practitioner (Buscemi et al. 2004; IOM 2004).

Jet lag:
For occasional short-term use (Herxheimer and Petrie 2009).

**Risk information**

Statement(s) to the effect of

**Caution(s) and warning(s)**

All uses except jet lag:
If symptoms persist for more than 4 weeks (chronic insomnia), consult your health care practitioner (Buscemi et al. 2004; IOM 2004; Dipiro et al. 2002).

All uses:
- Consumption with alcohol, other medications or natural health products with sedative properties is not recommended (Herxheimer and Petrie 2009; Holliman and Chyka 1997).
- If you have one of the following conditions, consult a health care practitioner prior to use:
  - asthma (Sutherland et al. 2003; Sutherland et al. 2002)
  - cardiovascular disease (IOM 2004; Scheer et al. 2004; Cagnacci et al. 2001b; GAO 2001; Lusardi et al. 2000; Arangino et al. 1999)
  - chronic kidney disease (IOM 2004)
  - depression (der Marderosian and Beuttlers 2009; IOM 2004; GAO 2001; Carman et al. 1976)
  - diabetes or hypoglycaemia (Peschke and Mühlbauer 2010; Cagnacci et al. 2001a; GAO 2001).
  - hormonal disorder (IOM 2004; Cagnacci et al. 2001b; GAO 2011).
  - immune system disease (der Marderosian and Beutters 2009; Carrillo-Vico et al. 2005; IOM 2004; Calvo et al. 2002; GAO 2001; Maestroni 1993)
  - liver disease (IOM 2004)
  - migraines (IOM 2004)
  - seizure disorders (Herxheimer and Petrie 2009; IOM 2004; Sheldon 1998)
If you are taking one of the following medications, consult a health care practitioner prior to use:

- anticoagulant (Herxheimer and Petrie 2009; Wirtz et al. 2008)
- anticonvulsant (IOM 2004)
- blood pressure medications (Herxheimer and Petrie 2009; Scheer et al. 2004; Lusardi et al. 2000)
- immunosuppressive medications (Lissoni et al. 1999; Maestroni 1993)
- sedative, hypnotic or psychotropic medications (IOM 2004; Holliman and Chyka 1997)
- steroids (GAO 2001)

**Contraindication(s)**

If you are pregnant or breastfeeding, do not use this product (IOM 2004).

**Known adverse reaction(s)**

- Mild gastrointestinal symptoms (nausea, vomiting, or cramping) have been known to occur in which case, discontinue use (Herxheimer and Petrie 2009).
- Rare allergic reactions have been known to occur in which case, discontinue use (Herxheimer and Petrie 2009).

**Non-medicinal ingredients**

Must be chosen from the current NHPD *Natural Health Products Ingredients Database* (NHPID) and must meet the limitations outlined in the database.

**Storage conditions**

Statement(s) to the effect of

No statement required.

**Specifications**

- The finished product specifications must be established in accordance with the requirements described in the NHPD *Quality of Natural Health Products Guide*.
- The medicinal ingredient must comply with the requirements outlined in the *Natural Health Products Ingredients Database* (NHPID). In addition, the medicinal ingredient may comply with the specifications outlined in the Melatonin monograph of the British Pharmacopoeia.

**References cited**


Citera G, Arias MA, Maldonado-Cocco JA, Lazaro MA, Rosemfflet MG, Brusco LI, Scheines EJ,


Suhner A, Schlagenhauf P, Johnson R, Tschopp A, Steffen R. Comparative study to determine


Sutherland ER, Martin RJ, Ellison MC, Kraft M. Immunomodulatory effects of melatonin in asthma. American Journal of respiratory and critical care medicine 2002;166:1055-1061.

Sutherland ER, Ellison MC, Kraft M, Martin RJ. Elevated serum melatonin is associated with the nocturnal worsening of asthma. Journal of Allergy and Clinical Immunology 2003;112(3):513-517.


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Blask DE, Sauer LA, Dauchy RT. Melatonin as a chronobiotic/anticancer agent: cellular, biochemical, and molecular mechanisms of action and their implications for circadian-based


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


Zee PC. Shedding light on the effectiveness of melatonin for circadian rhythm sleep disorders. Sleep 2010;33(12):1581-1582


Appendix 1: Examples of dosage preparations, frequencies of use and directions for use

All uses except jet lag:

Direction for use

All uses:
- Take once a day at or before bedtime (Murray et al. 2006; Kayumov et al. 2001; Zhdanova et al. 2001).
- Do not drive or use machinery for 5 hours after taking melatonin (Avery et al. 1998; Suhner et al. 1998b).

Jet lag:
0.5-10 mg, per day (Brown et al. 2009; Herxheimer and Petrie 2009; Suhner et al. 1998a)

Direction for use

- Take once a day at bedtime after darkness has fallen, while travelling and at the destination until adaptation to the new daily pattern (Herxheimer and Petrie 2009).
- Do not drive or use machinery for 5 hours after taking melatonin (Avery et al. 1998; Suhner et al. 1998b).
What is in this leaflet
This leaflet contains answers to some common questions about CIRCADIN.

It is particularly important that you read the sections "When to take it" and "How to take it" before you take this medicine. The leaflet does not contain all the information that is known about CIRCADIN. It does not take the place of talking to your doctor or pharmacist.

All medicines have risks and benefits. Your doctor has weighed the risks of you taking CIRCADIN against the benefits they expect it will have for you.

If you have any concerns about taking this medicine, ask your doctor or pharmacist.

Keep this leaflet with the medicine. You may need to read it again.

What CIRCADIN is used for
CIRCADIN is used to improve sleep quality and morning alertness in patients over 55 years of age with poor quality of sleep.

The active substance of CIRCADIN, melatonin (not of plant or animal origin), belongs to a group of naturally occurring hormones produced in the body.

Melatonin works by controlling the circadian rhythms and increasing the propensity to sleep.

Your doctor, however, may prescribe CIRCADIN for another purpose. Ask your doctor or pharmacist if you have any questions about why it has been prescribed for you.

This medicine is only available with a doctor’s prescription.

CIRCADIN is not addictive.

Before you take CIRCADIN

When you must not take it
Do not take CIRCADIN if you are allergic to it or any of the ingredients listed at the end of this leaflet.

Symptoms of an allergic reaction may include shortness of breath, wheezing or difficulty breathing, swelling of the face, lips, tongue or other parts of the body, or rash, itching or hives on the skin.

Do not take CIRCADIN if you have been drinking alcohol or intend to drink alcohol or believe that you may have alcohol, in your blood stream.

Do not take CIRCADIN if you are pregnant or breast-feeding. CIRCADIN has not been studied in pregnant or breast-feeding women.

Do not take it after the expiry date printed on the pack.
If you take it after the expiry date has passed, it may not work as well. The expiry date refers to the last day of the month.

Do not take it if the packaging is torn or shows signs of tampering.
If you are not sure whether you should start taking CIRCADIN talk to your doctor.

Before you start to take it
Tell your doctor if:
1. you have any allergies to any other medicines or any other substances, such as foods, preservatives or dyes.
2. you are pregnant or plan to become pregnant
3. you are breast-feeding or planning to breast-feed
4. you have, or have had the following medical conditions:
   • suffer from liver problems
   • suffer from kidney problems
   • If you suffer from an autoimmune disease
   • have a rare hereditary problem of galactose intolerance, the LAPP lactase deficiency or glucose-galactose malabsorption

Do not give CIRCADIN to a child or adolescent. There is no experience with its use in children or adolescents under 18 years old.

If you have not told your doctor about any of the above, so before you use CIRCADIN.

Taking other medicines
Tell your doctor if you are taking any other medicines, including any that you buy without a prescription from your pharmacy, supermarket or health food shop. Some medicines may affect the way other medicines work.

Some medicines and CIRCADIN may interfere with each other. These include:
• hypnotics and tranquilisers (e.g. benzodiazepine),
• fluvoxamine, thioridazine and imipramine (used to treat depression or psychiatric problems),
• oestrogen (contraceptives or hormone replacement therapy),
• cimetidine and psoralens (used to treat skin problems e.g. psoriasis)
• alcohol
• caffeine
The effect of adding CIRCADIN to other medicines used to treat insomnia has not been examined. It is not known if CIRCADIN will increase or decrease the effects of other treatments for insomnia.

Your doctor or pharmacist has more information on medicines to be careful with or avoid while taking CIRCADIN.

How to take CIRCADIN

How much to take
Take CIRCADIN only when prescribed by your doctor. The standard dose of CIRCADIN is one tablet once a day. There is no evidence that taking more than the recommended dose will increase the effect of CIRCADIN.

How to take it
Swallow your tablet whole with a full glass of water.
Do not crush, chew or divide your tablet.
Each CIRCADIN tablet has been specially designed to release the right dose of medicine while you sleep. If you crush, chew or divide the tablet they will not work properly.
Follow all directions given to you by your doctor carefully.

They may differ from the information contained in this leaflet.

If you do not understand the instructions on the box, ask your doctor or pharmacist for help.

When to take it
After food, 1-2 hours before you go to bed.

How long to take it
It is important that you continue taking CIRCADIN for as long as your doctor prescribes. CIRCADIN may be continued for up to thirteen weeks.

If you forget to take it
If you forget to take your tablet, take another as soon as you remember, before going to bed or wait until it is time for your next dose.
Do not take a double dose to make up for a forgotten dose.
If you are not sure what to do, talk to your doctor or pharmacist.

If you take too much (overdose)
Immediately telephone your doctor or Poisons Information Centre (In Australia 13 11 26 and in New Zealand 0800 POISON [0800 764 766]), or go to your nearest accident and emergency centre, if you think that you or anyone else may have taken too much CIRCADIN. Do this even if there are no signs of discomfort or poisoning.

While you are using CIRCADIN

Things you must do
If you are about to be started on any new medicine tell your doctor and pharmacist that you are taking CIRCADIN.

Tell any other doctors, dentists and pharmacists who treat you that you are taking this medicine.

If you become pregnant while taking CIRCADIN, stop taking the tablets and tell your doctor immediately.

Things you must not do
Do not give CIRCADIN to anyone else, even if they have the same condition as you.

Do not take more than the recommended dose unless your doctor tells you to.

Do not use this medicine to treat any other complaints unless your doctor tells you to.

Do not drink alcohol before or after taking this medicine

Things to be careful of
CIRCADIN rarely causes drowsiness, nevertheless it is not recommended to drive or operate machinery for 8 hours after you take it. Circadin does not impair morning alertness, but if you suffer from drowsiness during the day you should consult your doctor.

Side Effects
Tell your doctor or pharmacist as soon as possible if you do not feel well while you are taking CIRCADIN.

CIRCADIN has been shown to improve the sleep of most people aged over 55 years, but it may have unwanted side effects in a few people. All medicines can have side effects. Sometimes they are serious, but most of the time they are not. You may need medical treatment if you get some of the side effects.

Ask your doctor or pharmacist to answer any questions you may have.
Tell your doctor if you notice any of the following and they worry you.

These are considered to be uncommon side effects (i.e., likely to occur in fewer than 1 in 100 patients):

- Irritability, nervousness, restlessness, insomnia, abnormal dreams, anxiety, nightmares, migraine, lethargy, psychomotor hyperactivity (restlessness associated with increased activity), dizziness, somnolence (tiredness), headache, high blood pressure, (upper) abdominal pain, indigestion, mouth ulceration, dry mouth, nausea, hyperbilirubinaemia (changes in the composition of your blood which could cause yellowing of the skin or eyes (jaundice), inflammation of the skin (dermatitis), night sweats, pruritis (itching), rash, dry skin, pain in extremities, menopausal symptoms, asthenia (feeling of weakness), chest pain, excretion of glucose in urine, excess proteins in the urine, abnormal liver function and weight increase.

The following events are considered to be rare (i.e., likely to occur in fewer than 1 in 1,000 patients):

- Shingles, reduced number of white blood cells in the blood, decreased number of platelets in the blood, high level of fatty molecules in the blood, severe chest pain due to angina, feeling your heartbeat (palpitations), low serum calcium levels in the blood, low sodium levels in the blood, altered mood, aggression, agitation, crying, stress symptoms, disorientation, early morning awakening, increased sex drive, depressed mood, depression, loss of consciousness or fainting, memory impairment, disturbance in attention, dreamy state, restless legs syndrome, poor quality sleep, 'pins and needles' feeling (paresthesia) reduced visual acuity (visual impairment), blurred vision, watery eyes, dizziness when standing or sitting, vertigo, hot flushes, gastro-esophageal reflux, gastrointestinal disorder, blisters in the mouth, tongue ulceration, gastrointestinal upset, vomiting, abnormal bowel sounds, flatulence (wind), salivary hypersecretion (excess saliva production), halitosis (bad breath), abdominal discomfort, gastric disorder, inflammation of the stomach lining, eczema, erythema (skin rash), hand dermatitis, psoriasis, pruritic rash (itchy rash), nail disorder, arthritis, muscle spasms, neck pain, night cramps, increased duration of erection, inflammation of the prostate gland, tiredness, pain, thirst, passing large volumes or urine, presence of red blood cells in the urine, urination during the night, increased liver enzymes, abnormal blood electrolytes and abnormal laboratory tests.

Other side effects not listed above may also occur in some patients. Tell your doctor if you notice any other effects.

Do not be alarmed by this list of possible side effects. You may not experience any of them.

Keep CIRCADIN away from sunlight.

Keep the medicine in a cool dry place where the temperature stays below 25°C.

Do not store it or any other medicine in the bathroom, near a sink, or on a window-sill.

Do not leave it in the car.

Heat and damp can destroy some medicines.

Keep it where children cannot reach it.

A locked cupboard at least one-and-a-half metres above the ground is a good place to store medicines.

Disposal

If your doctor tells you to stop taking the tablets or the tablets have passed their expiry date, ask your pharmacist what to do with any that are left over.

Return any unused medicine to your pharmacist.

Product description

What CIRCADIN looks like

CIRCADIN 2 mg tablets are white to off-white round bi-convex shaped tablets.

CIRCADIN tablets are available in a 30 tablet pack and a 7 tablet sample pack.

Ingredients

Active ingredient

Each CIRCADIN 2 mg tablet contains 2 mg melatonin as the active ingredient.

Inactive ingredients:

- Ammonio methacrylate copolymer type B,
- calcium hydrogen phosphate,
- lactose,
- colloidal anhydrous silica,
- purified talc,
- magnesium stearate.
Database of Adverse Event Notifications - medicines

Medicine summary

You searched for the following 3 medicines between 01/01/1981 – 18/05/2016:

• Bioglan Melatonin (Melatonin)
• Circadin (Melatonin)
• Not specified (Melatonin)
Important information

The TGA uses adverse event reports to identify when a safety issue may be present. An adverse event report does not mean that the medicine is the cause of the adverse event. If you are experiencing an adverse event, or think you may be experiencing one, please seek advice from a health professional as soon as possible. The TGA strongly advises people taking prescription medicines not to change their medication regime without prior consultation with a health professional.

About the Database of Adverse Event Notifications (DAEN) - medicines

- The DAEN - medicines contains information from reports of adverse events that the TGA has received in relation to medicines including vaccines used in Australia.
- The DAEN - medicines does not contain all known safety information about a particular medicine. Please do not make an assessment about the safety of a medicine based on the information in the DAEN - medicines.

The TGA medicine safety monitoring program

More information about the DAEN - medicines and the TGA medicines safety monitoring program is available at:


You are encouraged to report an adverse event suspected of being related to a medicine used in Australia. Reports of adverse events in relation to medicines and vaccines can be reported using the 'blue card' reporting form, by phone and online <http://www.tga.gov.au/safety/problem.htm>.

Other useful sources of information on Australian medicines


Your health professional can also provide help and assistance on how to use medicines.

Information on medicines used in Australia is available from NPS MedicineWise <http://www.nps.org.au/>.

About the release of this information

While reasonable care is taken to ensure that the information is an accurate record of the adverse events reported to the TGA, the TGA does not guarantee or warrant the accuracy, reliability, completeness or currency of the information or its usefulness in achieving any purpose.

To the fullest extent permitted by law, including but not limited to section 61A of the Therapeutic Goods Act 1989, the TGA will not be liable for any loss, damage, cost or expense incurred in or arising by reason of any person relying on this information.

Results

Number of reports (cases): 65
(Multiple adverse events have been reported for some patients)

Number of cases with a single suspected medicine: 53
(The TGA thinks there is a possibility that the medicine caused the adverse event)

Number of cases where death was a reported outcome: 0
(These reports of death may or may not have been a result of taking a medicine)

<table>
<thead>
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<th>MedDRA system organ class</th>
<th>MedDRA reaction term</th>
<th>Number of cases</th>
<th>Number of cases with a single suspected medicine</th>
<th>Number of cases where death was a reported outcome</th>
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The TGA uses adverse event reports to identify when a safety issue may be present. An adverse event report does not mean that the medicine is the cause of the adverse event. If you are experiencing an adverse event, or think you may be experiencing one, please seek advice from a health professional as soon as possible. The TGA strongly advises people taking prescription medicines not to change their medication regime without prior consultation with a health professional. Please read all the important information at the beginning of this report.
### Footnotes

<table>
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<tr>
<th>MedDRA system organ class</th>
<th>MedDRA reaction term</th>
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**Footnotes**

1. A description of what, in general terms, was affected by the adverse event, as described by the Medical Dictionary for Regulatory Activities MedDRA (for example 'cardiac disorders')

2. A description of the adverse event as defined by MedDRA; these adverse events are grouped by system organ class. You can use the MedlinePlus medical dictionary [http://www.nlm.nih.gov/medlineplus/mplusdictionary.html](http://www.nlm.nih.gov/medlineplus/mplusdictionary.html) to look up terms.

3. The number of cases for which each type of adverse event was reported

4. Results show where a medicine is the only medicine suspected to be related to the adverse event

5. These reports of death may or may not have been the result of taking a medicine