CIRCADIN 2 mg

SCHEDULING STATUS:

S4

PROPRIETARY NAME (AND DOSAGE FORM):

CIRCADIN 2 mg (prolonged-release tablet)

COMPOSITION:

Each tablet contains 2 mg melatonin.

Inactive ingredients:

Ammonio methacrylate copolymer type B, (Eudragit RSPO), calcium hydrogen phosphate dehydrate, lactose monohydrate, magnesium stearate, silica, colloidal anhydrous (Aerosil 200), talcum.

PHARMACOLOGICAL CLASSIFICATION:

A 2.2 Sedatives, hypnotics

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Melatonin is a hormone produced by the pineal gland and is structurally related to serotonin.

The activity of melatonin at the melatonin 1 (MT1), melatonin 2 (MT2) and melatonin 3 (MT3) receptors is believed to contribute to its sleep promoting properties, as these receptors (mainly MT1 and MT2) are involved in the regulation of circadian rhythms and sleep regulation.

Pharmacokinetic properties:

Absorption:

The absorption of orally ingested melatonin is complete in adults and may be decreased by up to 50 % in the elderly. The kinetics of melatonin is linear over the range of 2-8 mg.

Bioavailability is in the order of 15 %. There is a significant first pass effect with an estimated first pass metabolism of 85 %. T_{max} occurs after 3 hours in a fed state. The rate of melatonin absorption and C_{max} following CIRCADIN 2 mg oral administration is affected by food. The presence of food delayed the absorption of the melatonin resulting in a later (T_{max} = 3,0 h versus T_{max} = 0,75 h) and lower peak plasma concentration in the fed state (C_{max} = 1020 pg/ml versus C_{max} = 1176 pg/ml).

Distribution

The in vitro plasma protein binding of melatonin is approximately 60 %. Melatonin is mainly bound to albumin, alpha1-acid glycoprotein and high density lipoprotein.

Biotransformation:

Experimental data suggest that isoenzymes CYP1A1, CYP1A2 and possibly CYP2C19 of the cytochrome P450 system are involved in melatonin metabolism. The principal metabolite is 6-sulphatoxy-melatonin (6-S-MT), which is inactive. The site of biotransformation is the liver. The excretion of the metabolite is completed within 12 hours after ingestion.

Elimination:

Terminal half-life (t½) is 3,5 - 4 hours. Elimination is by renal excretion of metabolites, 89 % as sulphated and glucuronide conjugates of 6-hydroxymelatonin and 2 % is excreted as unchanged melatonin.

Gender:

A 3-4 fold increase in C_{max} is apparent for women compared to men. A five-fold variability in C_{max} between different members of the same gender has also been observed. No pharmacodynamic differences between males and females were found despite differences in blood levels.

Special populations:

Elderly:

Melatonin metabolism is known to decline with age. Across a range of doses, higher AUC and C_{max} levels have been reported in older subjects compared to younger subjects, reflecting lower

metabolism of melatonin in the elderly. C_{max} levels around 500 pg/ml in adults (18-45) versus 1200 pg/ml in the elderly (55-69); AUC levels around 3000 pg/h/ml in adults versus 5000 pg/h/ml in the elderly.

Renal impairment:

There is no accumulation after repeated dosing. This finding is compatible with the short half-life in humans. The levels assessed in the blood of patients with end stage renal disease on chronic hemodialysis, at 23:00 (2 hours after administration) following 1 and 3 weeks of daily administration were 411,4 ± 56,5 and 432,0 ± 83,2 pg/ml respectively, and are similar to those found in healthy volunteers following a single dose of CIRCADIN 2 mg.

Hepatic impairment:

The liver is the primary site of melatonin metabolism and therefore, hepatic impairment results in higher endogenous melatonin levels. Plasma melatonin levels in patients with cirrhosis were significantly increased during daylight hours. Patients had a significantly decreased total excretion of 6-sulfatoxymelatonin compared with controls.

INDICATIONS:

CIRCADIN 2 mg is indicated for the short term (3 weeks) treatment of primary insomnia characterised by poor quality of sleep in patients who are aged 55 years or over.

CONTRA-INDICATIONS:

Hypersensitivity to melatonin or any of the excipients.

WARNINGS AND SPECIAL PRECAUTIONS:

No clinical data exist concerning the use of CIRCADIN 2 mg in individuals with autoimmune diseases. Therefore CIRCADIN 2 mg is not recommended for use in patients with autoimmune diseases.

Patients with rare hereditary problems of galactose intolerance, the LAPP lactase deficiency or glucose-glucose malabsorption should not take this medicine.

Driving and operating machines:

CIRCADIN 2 mg has minimal influence on the ability to drive and use machines. Nevertheless, patients should avoid engaging in hazardous activities (such as driving or operating machinery) after taking CIRCADIN 2 mg.

INTERACTIONS:

Pharmacokinetic interactions:

- Melatonin has been observed to induce CYP3A in vitro at supra-therapeutic concentrations. The clinical relevance of this finding is unknown. If induction occurs, this can give rise to reduced plasma concentrations of concomitantly administered medicines.
- Melatonin does not induce CYP1A enzymes in vitro at supra-therapeutic concentrations. Therefore interactions between melatonin and other active substances as a consequence of melatonin's effect on CYP1A enzymes are not likely to be significant.
- Melatonin's metabolism is mainly mediated by CYP1A enzymes. Therefore, interactions between melatonin and other active substances as a consequence of their effect on CYP1A enzymes is possible.
- Caution should be exercised in patients on fluvoxamine, which increases melatonin levels (17-fold higher AUC and a 12-fold higher serum C_{max}) by inhibiting its metabolism by hepatic cytochrome P450 (CYP) isoenzymes CYP1A2 and CYP2C19. The combination should be avoided.
- Caution should be exercised in patients on 5 or 8-methoxypsoralen (5 and 8-MOP), which increases melatonin levels, by inhibiting its metabolism.
- Caution should be exercised in patients on cimetidine, a CYP2D inhibitor, which increases melatonin levels by inhibiting its metabolism.
- Cigarette smoking may decrease melatonin levels due to induction of CYP1A2.
- Caution should be exercised in patients on oestrogens (e.g. contraceptive or hormone replacement therapy), which increase melatonin levels by inhibiting its metabolism by CYP1A1 and CYP1A2.
- CYP1A2 inhibitors such as quinolones may give rise to increased melatonin exposure.

- CYP1A2 inducers such as carbamazepine and rifampicin may give rise to reduced plasma concentrations of melatonin.
- There is a large amount of data available in the literature regarding the effect of adrenergic agonists/antagonists, opiate agonists/antagonists, antidepressants, prostaglandin inhibitors, benzodiazepines, tryptophan and alcohol, on endogenous melatonin secretion. Whether or not these active substances interfere with the dynamic or kinetic effects of CIRCADIN 2 mg or vice versa has not been studied.

Pharmacodynamic interactions:

- Alcohol should not be taken with CIRCADIN 2 mg, because it reduces the effectiveness of CIRCADIN 2 mg on sleep.
- CIRCADIN 2 mg may enhance the sedative properties of benzodiazepines and non-benzodiazepine hypnotics, such as zalepon, zolpidem and zopiclone.
- CIRCADIN 2 mg has been co-administered in studies with thioridazine and imipramine. No clinically significant pharmacokinetic interactions were found.

PREGNANCY AND LACTATION:

Safety in pregnancy and lactation has not been established. There are no clinical data available on use in pregnancy. Endogenous melatonin was measured in breast milk thus exogenous melatonin is probably secreted into human milk.

DOSAGE AND DIRECTIONS FOR USE:

The recommended dose in patients 55 years and older is 2 mg once daily, 1-2 hours before bedtime and after food. The dosage may be continued for 3 weeks.

Tablets should be swallowed whole.

Efficacy in patients younger than 55 years has not been demonstrated.

Paediatric use:

CIRCADIN 2 mg is not recommended for use in children and adolescents below age 18 due to insufficient data on safety and efficacy.

Renal insufficiency:

The effect of any stage of renal insufficiency on melatonin pharmacokinetics has not been studied.

Hepatic impairment:

There is no experience with CIRCADIN 2 mg in patients with liver impairment. Data demonstrates markedly elevated endogenous melatonin levels during daytime hours due to decreased clearance in patients with hepatic impairment. Therefore, CIRCADIN 2 mg is not recommended for use in patients with hepatic impairment.

SIDE EFFECTS:

The following adverse effects were reported in clinical trials and were defined as possibly, probably or definitely related to treatment.

Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100, < 1/10), uncommon (≥ 1/1000, < 1/100), rare (< 1/1000), very rare < 1/10000; not known (cannot be established from the available data).

System organ Class	**Very common**	**Common**	**Uncommon**	**Rare**
Infections and infestations				Herpes zoster
Blood and lymphatic disorders				Leukopenia Thrombocytopenia
Metabolism and nutrition disorders				Hypertriglyceridaemia
Psychiatric disorders			Irritability Nervousness Restlessness	Altered mood, aggression, agitation, crying, early morning awakening, increased libido.

			Insomnia Abnormal dreams.	
Nervous system disorders			Migraine, psychomotor hyperactivity, dizziness, somnolence	Memory impairment, disturbance in attention, poor quality sleep
Eye disorders				Reduced visual acuity, blurred vision, increased lacrimation.
Ear and labyrinth disorders				Positional vertigo.
Vascular disorders				Hot flush.
Gastro-intestinal disorders			Abdominal pain, constipation, dry mouth	Gastrointestinal disorder, gastrointestinal upset, vomiting, abnormal bowel sounds, flatulence, salivary hypersecretion, halitosis.
Hepatobiliary disorders			Hyper - bilirubinaemia	Hepatic enzyme increased, liver function test abnormal, laboratory test abnormal
Skin and subcutaneous tissue disorders			Hyperhidrosis	Eczema, erythema, pruritic rash, pruritus, dry skin, nail disorder, night sweats.
Musculoskeletal and				Muscle cramp, neck pain

connective tissue disorders				
Reproductive system and breast disorders				Priapism
General disorders and administration site conditions			Asthenia	Fatigue
Investigations			Increased weight	

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

No case of overdosage has been reported.

If overdosage occurs, drowsiness is to be expected. Clearance of the active substance is expected within 12 hours after ingestion. No special treatment is required.

IDENTIFICATION:

White to off-white, round biconvex tablet, with no imprint or break-line.

PRESENTATION:

The tablets are packed in white opaque PVC/PVdC/ aluminium blisters. One blister strip containing 20, 21 or 30 tablets are packed in a cardboard carton.

STORAGE CONDITIONS:

Store at or below 25 °C. Protect from light. Keep in the carton until required for use.

Keep out of reach of children.

REGISTRATION NUMBER

44/2.2/0001

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

TAKEDA (Pty) Ltd

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