▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at https://www.tga.gov.au/reporting-problems

AUSTRALIAN PRODUCT INFORMATION – IMMELA (MELATONIN) CAPSULES AND ORAL SOLUTION

1 NAME OF THE MEDICINE

Melatonin

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

IMMELA capsules contain 2 mg, 3 mg or 5 mg of melatonin.

IMMELA oral solution contains 1 mg/mL of melatonin.

Excipients with known effect:

Capsules:

Gelatin – May contain traces of sulfites

Oral Solution:

Sucralose

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Capsules:

2 mg: Opaque hard gelatin capsules with a white body and light blue cap.

3 mg: Opaque hard gelatin capsules with a white body and white cap.

5 mg: Opaque hard gelatin capsules with a light blue body and light blue cap.

Oral Solution:

A clear, colourless to yellowish solution.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Adult

Short-term treatment of jet lag in adults aged 18 and over.

Paediatric

Sleep disorders in children and adolescents aged 6 to 18 with neurodevelopmental disorders including autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD), where sleep hygiene measures have been insufficient.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

Adults

Jet lag

The recommended dose is 2 mg once daily taken at the preferred local sleep time. The dose may be increased to up to a maximum of 5 mg if the standard dose does not adequately alleviate symptoms. The lowest effective dose should be used.

IMMELA should be taken for the shortest period of time, with a maximum duration of 5 days.

Due to the potential for incorrectly timed intake of melatonin to have no effect, or an adverse effect, on re-synchronisation following jet lag, IMMELA should not be taken before 8pm or after 4am destination time.

Paediatrics

Neurodevelopmental disorders

The recommended starting dose is 2 mg once daily taken 30 minutes to 1 hour before bedtime. If an inadequate response has been observed, the daily dose should be increased to a maximum of 5 mg per day.

The patient should be monitored at regular intervals (at least every 6 months) to check that IMMELA is still the most appropriate treatment. After at least 3 months of treatment, the physician should evaluate the treatment effect and consider stopping treatment if no clinically relevant treatment effect is seen. If a lower treatment effect is seen after titration to a higher dose, the prescriber should first consider a down-titration to a lower dose before deciding on a complete discontinuation of treatment.

Method of Administration

Food can enhance the increase in plasma melatonin concentration (see Section 5.2). Intake of melatonin with carbohydrate-rich meals may impair blood glucose control for several hours (see Section 4.4). It is recommended that IMMELA is administered on an empty stomach and food is not consumed 1 h before and 1 h after intake of IMMELA.

Capsules:

IMMELA capsules should be swallowed whole with fluid.

Oral Solution:

A 10 mL graduated oral syringe with 0.5 mL graduations and a press-in bottle adapter are provided with the product.

1. Open the bottle and at first use, insert the press-in bottle adapter. The adapter will remain in the bottle.
2. Insert the syringe into the adapter, invert the bottle and draw out the required dose.
3. Return bottle to upright position and remove the filled syringe.
4. Empty the syringe into the patient’s mouth.
5. Replace the cap on the bottle and rinse the syringe.

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in Section 6.1.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Drowsiness

Melatonin may cause daytime drowsiness. Therefore, IMMELA should be used with caution if the effects of drowsiness are likely to be associated with a risk to patient safety.

Autoimmune Diseases

There is no data concerning the use of melatonin in patients with autoimmune diseases. Therefore, IMMELA is not recommended in patients with autoimmune diseases.

Seizure risk

Melatonin may increase seizure frequency in patients experiencing seizures (e.g. epileptic patients). Patients suffering from seizures must be informed about this possibility before using Melatonin 1mg/ml oral solution. Melatonin may promote or increase the incidence of seizures in children and adolescents with multiple neurological defects.

Sorbitol and propylene glycol

IMMELA oral solution, contains 140 mg sorbitol and 150 mg propylene glycol in each mL.

This medicinal product contains sorbitol. Patients with hereditary fructose intolerance (HFI) should not take/be given this medicinal product. The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account. The content of sorbitol in medicinal products for oral use may affect the bioavailability of other medicinal products for oral use administered concomitantly.

Use in hepatic impairment

Limited data indicates that daytime endogenous blood melatonin concentration is markedly elevated in patients with hepatic impairment due to reduced clearance. Therefore, IMMELA is not recommended for patients with hepatic impairment.

Use in renal impairment

Limited data is available for the use of melatonin in patient with renal impairment. Therefore, IMMELA is not recommended for patients with renal impairment.

Use in the elderly

Melatonin metabolism is known to decline with age. Across a range of doses, higher AUC and Cmax levels have been reported in older subjects compared to younger subjects, reflecting the lower metabolism in the elderly. Also, refer to Section 5.2 Pharmacokinetic properties, Elderly.

Paediatric use (under 6 years of age)

Efficacy and safety of IMMELA in children under 6 years of age has not been established.

Effects on laboratory tests

No information is available on the effect of melatonin on laboratory tests.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Melatonin is metabolised primarily through the CYP1A1 and CYP1A2 enzymes. As a result, drugs that affect CYP enzymes which are involved in melatonin's metabolism could potentially affect melatonin's exposure with or without potential clinical consequences. However, there is a limited data available in terms of melatonin's potential for pharmacokinetic interactions.

Hepatic enzymes - Melatonin has been observed to induce CYP3A in vitro at supra-therapeutic concentrations. The clinical relevance of the finding is unknown. If induction occurs, plasma concentrations of concomitantly administered drugs can be reduced.

Melatonin does not appear to 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:

Quinolones - CYP1A2 inhibitors such as quinolones may give rise to increased melatonin exposure.

Carbamazepine and rifampicin - CYP1A2 inducers such as carbamazepine and rifampicin may give rise to reduced plasma concentrations of melatonin.

Fluvoxamine - Caution should be exercised in patients on fluvoxamine, which increases melatonin levels (17-fold higher AUC and 12-fold higher serum Cmax) by inhibiting its metabolism by hepatic cytochrome P450 (CYP) isozymes CYP1A2 and CYP2C19. The combination should be avoided.

5- or 8-methoxypsoralen - Caution should be exercised in patients on 5- or 8-methoxypsoralen (5 and 8-MOP), which increases melatonin levels by inhibiting its metabolism.

Cimetidine - Caution should be exercised in patients on cimetidine, a CYP2D inhibitor which increases plasma melatonin levels by inhibiting its metabolism.

Oestrogens - Caution should be exercised in patients on oestrogens (e.g. contraceptives or hormone replacement therapy), which increase melatonin levels by inhibiting its metabolism by CYP1A1 and CYP1A2.

Thioridazine and imipramine - Melatonin has been co administered in studies with thioridazine and imipramine, active substances which affect the central nervous system. No clinically significant pharmacokinetic interactions were found in each case. However, melatonin co administration resulted in increased feelings of tranquillity and difficulty in

performing tasks compared to imipramine alone, and increased feelings of "muzzy-headedness" compared to thioridazine alone.

Hypnotics **-** Melatonin may enhance the sedative properties of benzodiazepines and non-benzodiazepine hypnotics, such as zaleplon, zolpidem and zopiclone. In a study of jet lag therapy the combination of melatonin and zolpidem resulted in a higher incidence of morning sleepiness, nausea, and confusion, increased impairment of attention, memory and coordination as well as reduced activity during the first hour after getting up, compared to zolpidem alone. The use of melatonin in combination with these drugs is not recommended.

Warfarin **-** Melatonin may increase the anticoagulation activity of warfarin. The combination of warfarin or other vitamin K antagonists with melatonin may require dose adjustment of the anticoagulant drugs and should be avoided.

Cigarette smoking **-** Cigarette smoking may decrease melatonin levels due to induction of CYP1A2.

Alcohol **-** Alcohol is a sedative with the ability to alter physical and mental functions. There is a potential for patients to have enhanced drowsiness when alcohol is co-administered with melatonin

Other **-** There is a large amount of data in the literature regarding the effect of adrenergic agonists/antagonists, opiate agonists/antagonists, antidepressant medicinal products, prostaglandin inhibitors, benzodiazepines, tryptophan and alcohol, on endogenous melatonin secretion. Whether or not these active substances interfere with the dynamic or kinetic effects of melatonin or vice versa has not been studied.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No significant effects on fertility or reproductive performance were observed in rats given oral melatonin prior to mating through to early gestation at doses over 900-fold the recommended clinical dose, based on surface area.

IMMELA is not recommended in women and men planning pregnancy.

Use in pregnancy – Pregnancy Category B3

No clinical data on exposed pregnancies are available. In view of the lack of clinical data, use in pregnant women and by women intending to become pregnant is not recommended.

Use in lactation

Endogenous melatonin has been detected in human breast milk, thus exogenous melatonin is likely excreted into human milk. The effects of melatonin on the nursing infant have not been

established. Therefore, breast-feeding is not recommended in women under treatment with melatonin

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies were identified which evaluated the impact of melatonin on the ability to drive or operate machinery. However, as melatonin may cause drowsiness, IMMELA is not recommended prior to driving and using machines until the effects are known.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the safety profile

A review of published clinical trials indicated that the most common adverse events in adults are somnolence, headache, dizziness, nausea and stomach cramps.

A review of published clinical trials indicated that the most common adverse events in children and adolescents are somnolence, headache, nausea, seizures, dizziness and hyperactivity.

Tabulated list of adverse reactions

The adverse reactions reported in Table 1 are those generally reported for melatonin in published clinical trials and spontaneous case reports.

The adverse reactions are reported according to MedDRA system organ classification and frequencies. Frequencies are defined as: Very common (≥ 1/10); Common (≥ 1/100 to <1/10); Uncommon (≥ 1/1,000 to <1/100); Rare (≥ 1/10,000 to <1/1,000); Very rare (<1/10,000), Not known (cannot be established from the available data).

Table 1: List of adverse reactions

System organ class	Very Common	Common	Uncommon	Rare	Very Rare	Not Known
Blood and lymphatic system disorders				Leucopoenia Thrombocyto-penia		
Cardiac Disorders				Palpitations Angina Pectoris		Tachycardia
Ear and labyrinth disorders						Vertigo
Eye Disorders				Visual acuity reduced		

				Vision blurred Lacrimation increased		
Gastrointestinal disorders		Nausea	Abdominal pain Upper abdominal pain Dyspepsia Dry mouth Vomiting	Flatulence Salivary hypersecretion Halitosis Gastro-oesophageal Reflux Disease Oral ulcers Gastritis		Diarrhoea Constipation
General disorders and administration site conditions			Malaise Chest pain Asthenia	Pain Thirst Fatigue		Pyrexia
Immune System Disorders						Hypersensitivity reaction
Infections and Infestations				Herpes Zoster		
Investigations			Weight increased	Blood electrolytes abnormal Elevated alkaline phosphatase level		Weight decreased Electrocardiogram QT interval abnormal
Metabolism and nutrition disorders				Hypertriglyceridaemia		Decreased appetite
Musculoskeletal and connective tissue disorders				Arthritis Muscle Spasms		Muscular weakness Joint swelling Myalgia Arthralgia
Nervous System disorders	Somnolence	Headache Dizziness	Paraesthesia Hyperactivity Lethargy Migraine	Syncope (fainting) Disorientation Memory impairment Restless legs syndrome		Temor Light headedness Seizure
Psychiatric disorders		Irritability	Nervousness Abnormal dreams	Mood altered		Suicide attempt/ideation

			Nightmares Anxiety Insomnia Restlessness	Aggressive behaviour Libido increased Depression		Libido decreased Hypnotic Effects Confusion Visual Disturbances
Renal and urinary disorders			Glycosuria Proteinuria	Polyuria Haematuria Nocturnal Enuresis		
Reproductive system and breast disorders				Priapism Prostatitis	Galactorrhoea	
Respiratory, thoracic and mediastinal disorders						Cough
Skin and subcutaneous tissue disorders			Dermatitis Dry Skin Rash Pruritus	Nail Disorder	Tongue oedema Oedema of the oral mucosa	Hyperhidrosis Night Sweats
Vascular disorders			Hypertension	Hot flushes		

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Ingestion of daily doses of up to 300 mg of melatonin did not cause clinically significant adverse reactions.

Drowsiness, headache, dizziness, and nausea are the most commonly reported signs and symptoms of high doses with oral melatonin. Flushes, abdominal cramps, diarrhoea, headache, and scotoma lucidum have been reported after ingestion of extremely high melatonin doses (3000 – 6600 mg) for several weeks.

In cases of overdose, general supportive measures should be employed. Gastric lavage and administration of activated charcoal can be considered.

Clearance of the active substance is expected within 12 hours of ingestion.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Melatonin Receptor Agonists, ATC code: N05CH01

Melatonin is a hormone and antioxidant. Melatonin secreted by the pineal gland is involved in the synchronisation of circadian rhythms to the diurnal light-dark cycle. Physiologically, melatonin secretion increases shortly after the onset of darkness, peaks at 2-4 and diminishes during the second half of the night. Peak melatonin secretion is almost diametrically opposite peak daylight intensity, with daylight being the primary stimulus for maintaining the circadian rhythmicity of melatonin secretion.

Melatonin has a hypnotic / sedative effect and increases propensity for sleep. Melatonin administered earlier or later than the nocturnal peak in melatonin secretion can, respectively, advance or delay the circadian rhythmicity of melatonin secretion.

Mechanism of action

The activity of melatonin at the MT1 and MT2 receptors is believed to contribute to its sleep-promoting properties via their distinct actions on the circadian clock. The MT1 receptors are thought to inhibit neuronal firing, while the MT2 receptors have been implicated in the phase-shifting response.

Clinical trials

Adults

Jet lag

Clinical evidence to support the use of IMMELA for the short-term treatment of jet lag in adults aged 18 and over is derived from 19 published reports. The below table summarises the patient populations, dosage regimens, efficacy data for the pivotal studies.

Table 2: Summary of key efficacy results for the treatment of jet lag

Publication	Patient Population	Dose and Duration of Treatment	Efficacy data	NHMRC level of evidence
Tortorolo 2015	Adults. Age range not specified	0.5 mg to 10 mg Duration not specified	In healthy individuals travelling across more than 5 time zones, jet lag symptom scores (0–100) were 27 and 45 points per 1000 patients with placebo and melatonin, respectively (mean difference −17.74, 95% CI −23.98 to −11.50).	I
Herxheimer 2002	Adults	0.5 to 8 mg 4 to 8 days	Melatonin reduced the symptoms of jet lag in eight of the ten trials. No differences were detected between daily doses of 0.5 mg and 5 mg melatonin (Suhner 1998a), except 5 mg may have a greater hypnotic effect than 0.5 mg. A higher dose of 8 mg is not clearly more effective than 5 mg (Claustrat 1992). The relative ineffectiveness of 2mg slow-release melatonin (Suhner 1998a) suggests that a pulse of melatonin, briefly giving a higher concentration in the blood, works better.	I
Beaumont 2004	19 to 47 years	5 mg 5 days	Melatonin significantly shortened sleep latency compared to placebo and SRC groups on nights 4-6 (p<0.05). Compared to placebo, stage 1 sleep was significantly decreased in the melatonin group on Night 1 (-8 min, p<0.05). Stage 2 sleep was significantly longer in the melatonin group compared to the placebo and slow-release caffeine groups on Night 3 (p<0.05). The rebound of slow-wave sleep/Stage 3 was significantly shorter on Night 3 in the melatonin group compared to placebo subjects (p<0.05). The subjective evaluation of sleep found subjects fell asleep earlier and slept longer on Night 1 in the melatonin group compared to the placebo group (p<0.05). Melatonin did not reduce daytime sleepiness.	II
Suhner 1998	20 to 65 years	0.5 and 5 mg 4 days	5 mg melatonin significantly improved sleep quality (p<0.05) shortened sleep latency (p<0.05), reduced fatigue (p<0.05) and daytime sleepiness (p<0.05) at the destination. The 0.5 dose was almost as effective as the 5 mg dose. Only the hypnotic properties, such as sleep latency, were significantly greater with melatonin 5 mg. The 2 mg controlled-release	II

Publication	Patient Population	Dose and Duration of Treatment	Efficacy data	NHMRC level of evidence
			formulation was not as effective as the 0.5 mg and 5 mg doses.	
Petrie 1993	25 to 52 years	5 mg 8 days	The retrospective self-rating of overall recovery was completed by 44 out of 52 subjects (85%) on day 6 of their arrival. A between-group comparison of the groups revealed subjects in the late melatonin group showed statistically significantly lower mean visual analogue ratings of jet lag than the early melatonin group and placebo group. The late melatonin group demonstrated significant improvements in overall sleep disturbance, recovery of energy and recovery of alertness compared to placebo or early melatonin. although this did not reach statistical significance for all tests	II
Petrie 1989	28 to 68 years	5 mg 7 days	The VAS self-ratings of jet lag for both outbound and inbound flights were consistently higher in the placebo group compared to the melatonin group. The retrospective rating of jet lag on day 10 revealed melatonin subjects reported less overall jet lag compared to placebo subjects: mean ± SD; 2.15 ± 0.99 and 3.40 ± 1.47, respectively, F=10.0, $p<0.01$. Similar results in favour of melatonin were found in the other day 10-retrospective ratings of time to normal sleep pattern, time to not feeling tired during the day, tine to normal energy level, all $p<0.05$. No difference in the amount of sleep between the groups was found from the day before departure to seven days after arrival.	II
Arendt 1987	29 to 68 years	5 mg 5 days	All subjects who took melatonin self-rated their jet lag as 17 or less and six of the nine subjects on placebo rated their jet lag as greater than 50 on the visual analogue scale (VAS). This difference was statistically significant ($p<0.01$) as calculated by a Fisher's exact test for small sample sizes. Longer sleep latencies in the placebo group compared with the melatonin group were found during the first week of return ($p<0.02$). Sleep quality was better in the melatonin group compared to the placebo group (days 3-5; $p<0.05$) on return and there was a trend for earlier wake up with melatonin on days	III-1

Publication	Patient Population	Dose and Duration of Treatment	Efficacy data	NHMRC level of evidence
			6 and 7 (p=0.0501). There was no change between groups in time of lights off. VAS-rated jet lag was positively correlated with individual mean sleep latency (r=0.7666; p<0.001); however, its correlation with mean sleep quality was negative (r=0.6214; p<0.001). There were no significant findings in the temperature data. Subjects in the melatonin group showed a tendency to be more alert than the placebo group in the first five days of return; however, this did not reach statistical significance (p<0.1). The between group difference was greatest at 18:00 (p=0.055) and 24:00 (p<0.02). There was no significant variation in the alertness of melatonin subjects during the day (p>0.1); however, marked time of day differences were observed in the placebo group (p<0.002). Baseline patterns of alertness were re-established by days 14 and 15. A greater overall improvement in self-rated mood was found in the melatonin group compared to the placebo group when they returned home (p=0.06). There were no interactive effects. No other effects of treatment, variables (day, time of day) or interactive effects, were found.	

Paediatrics

Neurodevelopmental disorders

Clinical evidence to support the use of IMMELA for the treatment of sleep disorders in children and adolescents aged 6 to 18 with neurodevelopmental disorders including autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD), where sleep hygiene measures have been insufficient, is derived from 24 published reports. The below table summarises the patient populations, dosage regimens, efficacy data for the pivotal studies.

Table 3: Summary of key efficacy results for the treatment of sleep disorders in children and adolescents with neurodevelopmental disorders

Publication	Patient Population	Dose and Duration of Treatment	Efficacy data	NHMRC level of evidence
McDonagh 2019	≤18 years	1 mg per day to 12 mg per day	In 17 studies melatonin showed a reduction in sleep latency (11-51 minutes), most	I

Publication	Patient Population	Dose and Duration of Treatment	Efficacy data	NHMRC level of evidence
		(median 4.8 mg) 1-13 weeks	trials found the difference to be statistically significant. In 16 trials melatonin improved sleep duration by a median of 33 minutes, most trials found the difference to be statistically significant.	
Abdelgadir 2018	≤18 years	0.1 to 10 mg per day 1-13 weeks	There was a statistically significant higher total sleep time in the melatonin group compared with the placebo group (mean difference 48.26min, 95%CI 36.79 to 59.73). A subgroup analysis in children with neurodisabilities and ASD showed higher TST with the use of melatonin (respectively mean difference 27.91, 95% CI 4.23 to 51.60 and 61.30, 95% CI 50.48 to 72.13). The pooled data synthesis showed that sleep onset latency is significantly improved by the use of melatonin (mean difference −28.97, 95% CI −39.78 to −18.17)	I
Beresford 2018	≤18 years	The dose ranges were 0.5–1 mg, 0.5–12 mg, 3–6 mg and 2–10 mg. Fixed dosages were 3 mg (n = 2), 5 mg (n = 4) and 9 mg. 10 days-12 weeks	There was a statistically significant increase in diary- and actigraphy-reported total sleep time for melatonin compared to placebo. Ten studies measured the time from bedtime to sleep onset and showed a statically significant decrease. The benefit was greatest for ASD studies in which there was a mean reduction of 50.9 minutes (95% CI -55.5 to -46.2) Five studies measuring sleep efficiency reported no significant difference between melatonin and placebo, however some studies may not have been sufficiently powered to detect and effect.	I
Cuomo 2017	1-18 years	0.75 mg to 10 mg per day Duration not specified	Melatonin was found to have a strong impact on sleep latency (average weighted rank (ARW) 187), sleep duration (AWR 116), bedtime resistance (AWR 187) and co-sleeping (AWR 165). Melatonin was also found to have a moderate effect (AWR ranging from 25 to 60) on longest sleep episode, night wakings, nocturnal activity, parasomnia, sleep disordered breathing, sleep anxiety and sleep problems NOS). A negative effect was reported for sleep efficiency (AWR -17).	I

Publication	Patient Population	Dose and Duration of Treatment	Efficacy data	NHMRC level of evidence
Rossignol 2011	Predominantly paediatric but ranging from 2-52	0.75 mg to 25 mg. 2 weeks to over 4 years	12 studies reported an overall improvement rate of 84.2% (95% CI 81.4-88.9) in sleep with melatonin. 13 studies reported some form of sleep improvement with melatonin use (sleep duration, number of night-time awakenings, and sleep onset latency). One study showed significant reduction in night terrors, while two other studies reported a decrease in screaming in the middle of the night. Six studies reported improvements in daytime behaviour in some children with ASD.	I

5.2 PHARMACOKINETIC PROPERTIES

Melatonin is a small, amphiphilic molecule (molecular weight 232 g/mol) active in its parent form. Melatonin is synthesised in the human body from tryptophan via serotonin. Small quantities are obtained via diet. Data summarised below are from studies that generally involved healthy men and women, primarily young and middle-aged adults.

Absorption

Orally administered melatonin is almost completely absorbed. Oral bioavailability is ~ 15%, owing to first-pass metabolism of ~ 85%. Plasma Tmax is ~ 50 minutes. A 3 mg dose of immediate- release melatonin raises plasma melatonin Cmax to ~ 3400 pg/mL, which is ~ 60-times the nocturnal (endogenous) plasma melatonin Cmax, though both endogenous- and exogenous Cmax show considerable inter-individual variation.

Data on the effect of intake of food at or around the time of intake of melatonin on its pharmacokinetics are limited, though suggest that concomitant food intake may increase bioavailability almost 2-fold. Food appears to have a limited effect on Tmax for immediate-release melatonin. This is not expected to affect the efficacy or safety of IMMELA.

Plasma melatonin Cmax and AUC increase in a directly proportional, linear manner for oral doses of immediate-release melatonin in the range 1 – 6 mg whereas Tmax and plasma T½ remain constant.

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. The binding to the other serum proteins is insignificant. The melatonin binding was constant over the range of

the studied concentrations in serum. Literature data indicates that melatonin is distributed in all body fluids and is accessible at all tissues.

Metabolism

Melatonin is mainly metabolised by the liver. Experimental data suggest that the cytochrome P450 enzymes CYP1A1 and CYP1A2 are primarily responsible for melatonin metabolism, with CYP2C19 of minor importance. Melatonin is primarily metabolised to 6-hydroxymelatonin (constituting ~ 80 – 90% of melatonin metabolites recovered in the urine). N-acetylserotonin appears to be the primary minor metabolite (constituting ~ 10% of melatonin metabolites recovered in the urine). Melatonin metabolism is very rapid, with plasma 6-hydroxymelatonin level rising within minutes of exogenous melatonin entering the systemic circulation. 6-hydroxymelatonin undergoes sulphate conjugation (~ 70%) and glucuronide conjugation (~ 30%) prior to excretion.

Excretion

Plasma elimination half-life (T½) is ~ 45 minutes (normal range ~ 30 – 60 minutes) in healthy adults. The half-life, on average, is comparable or slightly shorter in children compared to adults. Dosage once daily in combination with the short half-life means minimal accumulation of melatonin during regular treatment. Melatonin metabolites are mainly eliminated by the urine, ~ 90% as sulphate and glucuronide conjugates of 6-hydroxymelatonin. Less than ~ 1% of a melatonin dose is excreted unchanged in urine.

Gender

Limited data suggest that Cmax and AUC following ingestion of immediate-release melatonin may be higher (potentially roughly double) in women compared to men, however a large variability in the pharmacokinetics is observed. Plasma melatonin half-life does not appear to be significantly different in men and women.

Pre-pubertal children

Limited data suggests that prepubertal children metabolise melatonin faster than adults and, display a significantly shorter T½ and AUC compared to adult patients.

Elderly

Data from other formulations of melatonin indicate that the absorption of orally ingested melatonin may be decreased up to 50% in the elderly.

Melatonin metabolism is known to decline with age. Across a range of doses, higher AUC and Cmax levels have been reported in older subjects compared to younger subjects, reflecting the lower metabolism of melatonin in the elderly. Cmax levels around 500 pg/mL in adults (18-45) versus 1200 pg/mL in the elderly (55-65); AUC levels around 3,000 pg*h/mL in adults versus 6000 pg*h/mL in the elderly.

Hepatic Impairment

The liver is the primary site of melatonin metabolism and therefore, hepatic impairment results in higher endogenous melatonin levels.

Limited data indicates that daytime endogenous blood melatonin concentration is markedly elevated in patients with cirrhosis due to reduced clearance.

Renal Impairment

Decreased renal function is no expected to influence the elimination of melatonin as <1% of the dose is excreted unchanged in the urine. Melatonin is primarily excreted as metabolites; plasma levels of melatonin metabolites can be expected increase in patients with more advanced renal impairment.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Results from a standard battery of in vitro and in vivo assays showed no evidence of a genotoxic potential for melatonin.

Carcinogenicity

An oral lifetime carcinogenicity study with melatonin in rats showed an increased incidence of thyroid follicular cell adenomas in males at doses around 700-fold the recommended clinical dose, based on body surface area. No neoplastic tissue histopathology was examined at lower doses and therefore the no-effect dose could not be determined. These effects were associated with liver enzyme induction in this species and are unlikely to be relevant to humans.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Capsules:

- Microcrystalline cellulose
- Povidone
- Maltodextrin
- Magnesium stearate
- Titanium dioxide
- Indigo carmine (2 mg and 5 mg only)
- Gelatin

Oral Solution:

- Propylene glycol
- Sorbitol solution (70 per cent) (non-crystallising)
- Sucralose
- Strawberry flavour TEG 10315784 (ARTG PI No. 144274)
- Hydrochloric acid
- Purified water

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Capsules

Store below 25°C. Store in outer carton to protect from light.

Oral Solution

Store below 25°C. Use within 2 months of opening. Store in original package in order to protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

Capsules

PVC/PVDC/Al blister pack with 30 capsules.

IMMELA is also available as a starter pack with 10 capsules.

Oral Solution

A 150 mL Type III amber glass bottle, with a HDPE child-resistant, tamper-evident screw cap, bottle adapter and 10 mL graduated dosage syringe.

Not all strengths or pack sizes may be available.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

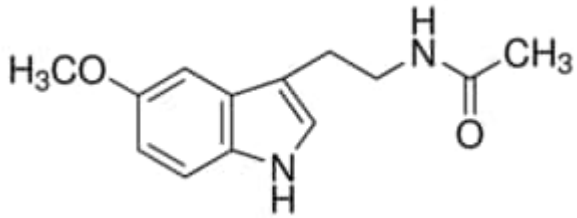
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Chemical name: N-[2-(5-Methyloxy-1H-indol-3-yl)ethyl]acetamide

Chemical structure:



Molecular formula: $C_{13}H_{16}N_2O_2$

Molecular weight: 232.27

CAS number

73-31-4

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4: Prescription Only Medicine

8 SPONSOR

Link Medical Products Pty Ltd
5 Apollo Street
Warriewood
NSW, 2102
Australia
Ph: 1800 181 060
linkhealthcare.com.au

9 DATE OF FIRST APPROVAL

27 October 2023

10 DATE OF REVISION

Summary table of changes

Section changed	Summary of new information