SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Aritonin 2 mg film-coated tablets
Aritonin 3 mg film-coated tablets
Aritonin 4 mg film-coated tablets
Aritonin 5 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 2 mg, 3 mg, 4 mg or 5 mg melatonin.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

2 mg: White/off-white to beige, biconvex, round film-coated tablet with a score line, marked “2” on one side. Diameter: 8 mm.
The tablet can be divided into equal doses.

3 mg: White/off-white to beige, biconvex, round film-coated tablet with a score line on one side. Diameter: 8 mm.
The tablet can be divided into equal doses.

4 mg: White/off-white to beige, biconvex, round film-coated tablet with a score line, marked “4” on one side. Diameter: 8 mm.
The tablet can be divided into equal doses.

5 mg: White/off-white to beige, biconvex, round film-coated tablets with a score line, marked “5” on one side. Diameter: 8 mm.
The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[Invented name] is indicated for:
- Short-term treatment of jet lag in adults (see section 5.1).
- Insomnia in children and adolescents aged 6–17 years with ADHD where sleep hygiene measures have been insufficient.

4.2 Posology and method of administration

Posology
Adults with jet lag
The recommended dose is 1–5 mg for a maximum of five days.

The dose should be taken at the time of destination bedtime (local time) for journeys of 5 time zones or longer, especially when traveling in an easterly direction.

Due to the potential for incorrectly timed intake of melatonin to have no effect, or an adverse effect, on re-synchronisation following jet lag, [Invented name] should not be taken before 20:00 hr or after 04:00 hr at destination.

As alcohol can impair sleep and potentially worsen certain symptoms of jet lag (e.g. headache, morning fatigue, concentration) it is recommended that alcohol is not consumed when taking [Invented name].

A maximum of 16 treatment cycles may occur per year.

Insomnia in children and adolescents with ADHD
Treatment should be initiated by physicians experienced in ADHD and/or paediatric sleep medicine. When treating insomnia in children and adolescents, melatonin should only be administered after other treatable causes of insomnia have been ruled out by appropriate specialist investigation and non-pharmacological measures have been insufficient.

Recommended starting dose of [Invented name]: 1–2 mg 30–60 minutes before bedtime.

The dose of melatonin can be increased by 1 mg every week until effect up to a maximum 5 mg per day, independent of age. The lowest effective dose should be sought.

Limited data are available for up to 3 years of 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. The patient should be monitored at regular intervals (at least every 6 months) to check that [Invented name] is still the most appropriate treatment. During ongoing treatment, especially if the treatment effect is uncertain, discontinuation attempts should be done regularly, e.g. once per year.

If the sleep disorder has started during treatment with medicinal products for ADHD, dose adjustment or switching to another product should be considered.

Special populations

Elderly

As the pharmacokinetics of melatonin (immediate release) is comparable in young adults and elderly persons in general, no specific dosage recommendations for elderly persons are provided (see section 5.2).

Renal impairment
The effect of any stage of renal impairment on melatonin pharmacokinetics has not been studied. Caution should be used when melatonin is administered to patients with renal impairment.

Hepatic impairment
Limited data indicate that plasma clearance of melatonin is significantly reduced in patients with liver cirrhosis.
Melatonin is not recommended in patients with moderate or severe hepatic impairment (see section 5.2).

Children below 6 years of age
[Invented name] is not recommended for children below 6 years with ADHD.

Method of administration
Oral use.
The tablet can be crushed and mixed with water directly before the 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 food is not consumed 2 h before and 2 h after intake of [Invented name].

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

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

Elderly
Exposure levels to melatonin after oral administration in young and moderately older adults are comparable. It is unclear if significantly older persons are especially sensitive to exogenous melatonin. Caution should therefore be exercised in treatment of this age group and individual dosage is recommended.

Immunological diseases
Occasional case reports have described exacerbation of an autoimmune disease in patients taking melatonin. There are no data regarding use of melatonin tablets in patients with autoimmune diseases. Melatonin is not recommended in patients with autoimmune diseases.

Epilepsy
Melatonin has been reported to increase, decrease, and have no effect on seizure frequency. Because of the uncertainty of the effect of melatonin on epileptic seizures, some caution should be exercised for use in people with epilepsy.

Diabetes
Limited data suggest that melatonin taken in close proximity to ingestion of carbohydrate-rich meals may impair blood glucose control for several hours. Melatonin tablets should be taken at least 2 hours before and at least 2 hours after a meal; ideally at least 3 hours after meal by persons with significantly impaired glucose tolerance or diabetes.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions
Melatonin is mainly metabolised via CYP1A enzymes. Interactions between melatonin and other active substances that affect CYP1A enzymes are therefore possible.

CYP1A2 inhibitors
CYP1A2 inhibitors may increase the plasma concentration of melatonin considerably. Caution must be observed in patients who are treated with fluvoxamine because this medicinal product increases the melatonin content (17-fold higher AUC and 12-fold higher Cmax in serum) by inhibiting its metabolism via CYP1A2 and CYP2C19. This combination must be avoided.

Caution must be observed for patients who are treated with oestrogens (e.g. hormonal contraceptives or hormone replacement therapy), which increase the melatonin content (a 4–5-fold increase for combined contraceptives containing ethinylestradiol and gestagen).

An increase in the plasma concentration of melatonin is expected through interaction with moderately pronounced inhibitors of CYP1A2. Caution should therefore be observed in patients who take 5- or 8-Methoxypsoralen (5- or 8-MOP), cimetidine or caffeine.

Caution should be observed in patients who take cimetidine because this agent increases the content of melatonin in plasma by inhibiting its metabolism.

CYP1A2 inducers
CYP1A2 inducers can reduce the plasma concentration of melatonin.

Dose adjustment of melatonin may be needed if given concomitantly with the following CYP1A2 inducers: carbamazepine, phenytoin, rifampicin, omeprazole, and cigarette smoking (halved exposure compared to after 7 days of smoking abstinence).

Pharmacodynamic interactions
Adrenergic agonists/antagonists, opiate agonists/antagonists, antidepressants, prostaglandin inhibitors, tryptophan and alcohol affect the endogenous secretion of melatonin in the epiphysis, but do not affect the metabolism of melatonin. It is not known if these interactions are of clinical significance.

Alcohol
Alcohol should not be used concomitantly with melatonin since it may reduce the effect of melatonin on sleep.

Nifedepine
Melatonin may reduce the hypotensive effect of nifedipine. Caution must be taken during concomitant use of melatonin and adjustment of the nifedipine dose may be needed. As it is not known if this is a class effect, caution should be exercised when combining melatonin and other calcium antagonists.

Warfarin
It has been reported in case reports that concomitant use of melatonin and vitamin K antagonists such as warfarin can lead to either increased or decreased prothrombin levels, and a study has shown decreased levels of factor VIII:C and fibrinogen. The combination of warfarin and other vitamin K antagonists with melatonin may require dose adjustment of the anticoagulant drugs and should be avoided.

Bensodiazepine-related hypnotics
Melatonin may enhance the sedative properties of benzodiazepine-related hypnotics, e.g. zolpidem. Concomitant treatment with melatonin should be avoided.

NSAIDs
Prostaglandin synthesis inhibitors (NSAIDs) such as acetylsalicylic acid and ibuprofen, taken in the evening, may suppress endogenous melatonin levels. If possible, administration of NSAIDs should be avoided in the evening.

Beta-blockers
Beta-blockers may suppress the endogenous melatonin and should therefore be administered in the morning.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no data from the use of melatonin in pregnant women. Animal studies are incomplete regarding effects on pregnancy, embryonic / fetal development, childbirth and postnatal development (see section 5.3). Exogenous melatonin readily crosses the human placenta. Considering the lack of clinical data, treatment with [Invented name] is not recommended during pregnancy or in women of childbearing potential not using contraceptives.

Breast-feeding
Data from animal studies indicate maternal transfer of melatonin to the foetus via the placenta or in the milk. Endogenous melatonin has also been measured in breast milk from breast-feeding women, and therefore exogenous melatonin is most likely also excreted in human milk. Melatonin is therefore not recommended to breastfeeding women.

Fertility
No adequate data on the effect of melatonin on human fertility are available. Animal studies are incomplete in terms of effects on fertility. High doses of melatonin and use for longer periods than indicated may compromise fertility in humans.

4.7 Effects on ability to drive and use machines

Melatonin has moderate effect on the ability to drive and use machines. Melatonin may cause drowsiness and should therefore be used with caution if the effects of drowsiness are likely to be associated with a safety risk.

4.8 Undesirable effects

Summary of the safety profile
Melatonin causes few, and no serious, adverse reactions in the short term, up to three months.
Long-term effects are poorly studied. Reported adverse reactions to melatonin are mainly headache, nausea and fatigue in both adults and children. These adverse reactions are however also common for placebo-treated patients in presented clinical studies and there is no significant difference between patients who received active treatments and placebo in these studies.
No common or very common adverse reactions have been reported.

Adverse reactions in adults compiled according to the MedDRA classification of organ systems are presented within each of the following frequency conventions: Very common (≥ 1/10); Common (≥ 1/100, < 1/10); Uncommon (≥ 1/1 000, < 1/100); Rare (≥1/10 000, <1/1 000); Very rare (<1/10 000); Not known (cannot be estimated from the available data).

Infections and infestations Rare	Herpes zoster
Blood and lymphatic system disorders Rare	Leukopenia, thrombocytopenia
Immune system disorders Not known (cannot be estimated from the available data)	Hypersensitivity reaction
Metabolism and nutrition disorders Rare Not known (cannot be estimated from the available data)	 Hypertriglyceridemia, hypocalcaemia, hyponatraemia Hyperglycaemia
Psychiatric disorders Uncommon Rare Not known (cannot be estimated from the available data)	 Irritability, nervosity, restlessness, insomnia, abnormal dreams, nightmares, anxiety Altered mood, aggression, agitation, crying, stress symptoms, disorientation, early morning awakening, increased libido, depressed mood, depression Hallucinations
Nervous system disorders Common Uncommon Rare	 Headache, somnolence Migraine, lethargy, psychomotor hyperactivity, dizziness Syncope, memory impairment, attention disturbances, dreamy state, restless legs syndrome, poor quality sleep, paraesthesia

Eye disorders Rare	Impaired visual acuity, blurred vision, increased lacrimation
Ear and labyrinth disorders Rare	Positional vertigo
Cardiac disorders Rare	Angina pectoris, palpitations
Vascular disorders Uncommon Rare	Hypertension Hot flushes
Gastrointestinal disorders Uncommon Rare	Abdominal pain, upper abdominal pain, dyspepsia, mouth ulcers, dry mouth, nausea Gastro-oesophageal reflux disease, gastrointestinal disorders, blisters in oral mucosa, tongue ulcers, gastrointestinal upset, vomiting, abnormal bowel sounds, flatulence, hypersalivation, halitosis, abdominal discomfort, gastric disorders, gastritis
Hepatobiliary disorders Uncommon	Hyperbilirubinemia
Skin and subcutaneous tissue disorders Uncommon Rare Not known (cannot be estimated from the available data)	Dermatitis, night sweats, pruritus, rash, generalised pruritus, dry skin Eczema, erythema, hand dermatitis, psoriasis, generalised rash, pruritic rash, nail disorders Angioedema, swollen mouth, swollen tongue
Musculoskeletal and connective tissue disorders Uncommon Rare	Pain in extremities Arthritis, muscle spasms, neck pain, night cramps
Renal and urinary disorders Uncommon Rare	Glycosuria, proteinuria Polyuria, haematuria, nocturia
Reproductive system and breast disorders Uncommon Rare	Menopausal symptoms Priapism, prostatitis

Not known (cannot be estimated from the available data)	Galactorrhoea
General disorders and administration site conditions Uncommon Rare	 Asthenia, chest pain Fatigue, pain, thirst
Investigations Uncommon Rare	 Abnormal liver function tests, weight increase Elevated liver enzyme, abnormal blood electrolytes, abnormal laboratory values

Paediatric population
A low frequency of in general mild adverse reactions have been reported in the paediatric population. The number of adverse reactions has not differed significantly between children who have received placebo compared to melatonin. The most common adverse reactions were headache, hyperactivity, dizziness and abdominal pain. No serious adverse reactions have been observed.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in Appendix V.

4.9 Overdose

Drowsiness, headache, dizziness, and nausea are the most commonly reported signs and symptoms of overdose with oral melatonin.

Daily doses of 20-50 mg as well as 300 mg in up to 2 years have been reported in the literature, without any clinically significant adverse reactions.

One dose of 250 mg taken 4 times daily during 25-30 days have only been reported to cause drowsiness/sleepiness. Also, in several cases of reported overdosing, mildly to moderately severe somnolence was the most commonly reported adverse reaction.

After doses of 3.0-6.6 grams for 15-36 days, 6 of 11 patients reported somnolence during daytime and 4 of 11 patients reported stomach cramps, diarrhoea or migraine headaches.

Clearance of the active substance is expected within 12 hours of ingestion. A physician should assess if conventional overdose measures should be taken.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Hypnotics and sedatives, melatonin receptor agonists, ATC code: N05CH01.

Melatonin is a hormone produced by the pineal gland. It is structurally related to serotonin. Melatonin secretion increases shortly after dark, reaching its peak between 2 am and 4 am and decreases during the latter half of the night. Melatonin is involved in controlling the circadian rhythm and adaptation to the light-dark cycle. Melatonin is also associated with a sedative effect and an increased propensity for sleep.

Mechanism of action

Melatonin's activity at the MT1 and MT2 receptors are considered to contribute to its effect on sleep because these receptors are involved in regulating circadian rhythm and sleep.

Pharmacodynamic effects
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. Administration of melatonin at bedtime (between 22:00 and 24:00 hr) at destination following rapid transmeridian travel (aircraft flight) hastens resynchronisation of circadian rhythmicity from 'departure time' to 'destination time', and ameliorates the collection of symptoms known as jet lag that are a consequence of such de-synchronisation.

Clinical efficacy and safety
Typical symptoms of jet lag are sleep disturbances and daytime tiredness and fatigue, though mild cognitive impairment, irritability, and gastrointestinal disturbances may also occur.

Jet lag is worse the more time-zones crossed, and is typically worse following eastward travel.

Eight of ten clinical trials found that melatonin, taken close to the target bedtime at the destination (10 pm to midnight), decreased jet lag from flights crossing five or more time zones. The benefit is likely to be greater the more time zones are crossed, and less for westward flights. Daily doses of melatonin between 0.5 and 5 mg are similarly effective, except that people fall asleep faster and sleep better after 5 mg than 0.5 mg.

Clinical trials have found melatonin to reduce patient-assessed overall symptoms of jet lag by ~44%, and to shorten the duration of jet lag. In 2 studies of flights over 12 time-zones melatonin effectively reduced the duration of jet lag by ~33%. Due to the potential for incorrectly timed intake of melatonin to have no effect, or to cause an adverse effect, on re-synchronisation of circadian rhythmicity/jet lag, melatonin should not be taken before 20:00 hr or after 04:00 hr at destination.

Adverse reactions reported in jet lag studies involving melatonin doses of 0.5 to 8 mg were typically mild, and often difficult to distinguish from symptoms of jet lag. Transient drowsiness/sedation, headache and dizziness/disorientation were reported; these same adverse reactions, plus nausea, are those typically associated with short-term use of melatonin in reviews of the safety of melatonin in humans.

Paediatric population
Melatonin treatment has been studied in a 4-week randomized, double-blind, placebo-controlled study conducted in 105 children between 6-12 years of age, with ADHD and chronic sleep onset insomnia (van der Heijden KB et al. 2007). Participants received melatonin (3 mg when body weight <40 kg [n = 44]; or 6 mg when body weight >40 kg [n = 9]) in fast-release tablets or placebo.
Mean actigraphic estimate of sleep onset advanced by 26.9 ± 47.8 minutes with melatonin, whereas there was a delay of 10.5 ± 37.4 minutes with placebo ($p < 0.0001$). 48.8% of children who received melatonin showed an advance of sleep onset >30 minutes compared to 12.8% with placebo ($p = 0.001$). There was an increase in mean total time asleep of 19.8 ± 61.9 minutes with melatonin and a decrease of 13.6 ± 50.6 minutes with placebo ($p = 0.01$). As compared with placebo, the melatonin group showed a decrease in sleep latency ($p = 0.001$) and increase in sleep efficiency ($p = 0.01$). The mean score on sleep log item difficulty falling asleep decreased by 1.2 ± 1.3 points (35.3% of baseline) with melatonin and by 0.1 ± 0.8 points (4.3% of baseline) with placebo ($p < 0.0001$).
There was no significant effect on behaviour, cognition, and quality of life. There were no discontinuations or withdrawals caused by adverse events.

5.2 Pharmacokinetic properties

Absorption
Absolute bioavailability of melatonin has been estimated in two studies to average 13% of the given dose via solution and 14–16% of the given dose via tablet. Maximum concentration of orally administered melatonin occurs after 15–90 minutes (median T_{max} = 52 min).

Maximum concentration and exposure of melatonin after oral dosing of tablets increases proportionally to the dose from 0.25 up to 10 mg.

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 the absorption almost 2-fold. Food appears to have a limited effect on t_{max} for immediate-release melatonin. This is not expected to affect the efficacy or safety of [Invented name], however, it is recommended that food is not consumed approximately 2 h before and 2 h after intake of melatonin.

Distribution
The *in vitro* plasma protein binding of melatonin is approximately 60%.

Biotransformation
Melatonin is mainly eliminated by hydroxylation to 6-hydroxymelatonin in the liver, primarily mediated by CYP1A2 (to a lesser extent by CYP1A1). Quantitatively less important O-demethylation to N-acetyl-5-hydroxytryptamine mediated by CYP2C19 occurs. 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.

Elimination
Plasma elimination half-life ($T_{½}$) 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.

Gender
A higher exposure and maximum plasma concentrations have been reported in women compared with men who received melatonin orally, however, a great variability in the pharmacokinetics has been observed. Melatonin's half life in plasma does not seem to differ significantly between men and women. No dose adjustment is needed for women.

Special populations
Elderly
In a comparative study of serum melatonin with and without exogenous supplementation, lower concentrations were found in moderately older adults without treatment, while a trend toward higher concentrations was observed compared to healthy younger adults after treatment. The difference during treatment was not statistically significant; the same dosage may be recommended for moderately older as for younger adults.

Hepatic impairment
Limited data indicate that the daytime endogenous blood melatonin concentration is markedly elevated in patients with liver cirrhosis, probably due to reduced clearance (metabolism) of melatonin.
Serum $t_{½}$ for exogenous melatonin in cirrhosis patients was double that of controls in a small study. As the liver is the primary site of melatonin metabolism, hepatic impairment can be expected to result in increased exposure to exogenous melatonin.

Renal impairment
No studies have been performed on the effect of melatonin's pharmacokinetics at any stage of renal impairment, see under heading 4.2 Special populations.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on limited studies of repeated dose toxicity, genotoxicity and reproductive toxicity.

A study in pregnant rats did not show direct or indirect harmful effects with respect to pregnancy, foetal survival or foetal development.

Data from animal studies indicate that melatonin is transmitted to the foetus via the placenta and to breast milk.
There are no safety studies in juvenile animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose, microcrystalline (E 460)
Maltodextrin
Silicon dioxide, colloidal, anhydrous (E 551)
Magnesium stearate (E 470b)
Hypromellose (E 464)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

[Invented name] 2 mg and 3 mg:
Do not store above 30 °C.
Store in the original package in order to protect from light.

[Invented name] 4 mg and 5 mg:
Store in the original package in order to protect from light.

6.5 Nature and contents of container

HDPE container (white polyethylene bottle) with HDPE/LDPE lid (with safety seal) containing desiccant.

Pack sizes
10, 30, 50, 60, 90, 100 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

2025-01-07