SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

adaflex ava 0.5 mg tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 tablet contains 0.5 mg melatonin.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

All strengths: White to almost white, round, biconvex tablets, diameter 8 mm.

adaflex ava 0.5 mg: marked 0.5 on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

adaflex ava 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 attention deficit hyperactivity disorder (ADHD), where sleep hygiene measures have been insufficient.

4.2 Posology and method of administration

Posology

Jet lag in adults

The standard dose of adaflex ava tablets is 3 mg daily for a maximum of 5 days. The daily dose of melatonin, in the range of 0.5 mg to 5 mg, may be gradually adjusted up to 5 mg for a maximum of 5 days, if symptoms are not sufficiently relieved by the standard dose. The dose that adequately alleviates symptoms should be taken for the shortest period.

The first dose should be taken on arrival at destination at the habitual bedtime (at local time).

Due to the potential for incorrectly timed intake of melatonin to have no effect, or an adverse effect, on re-synchronisation following jet lag, adaflex ava tablets 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 adaflex ava tablets (see section 4.5).

adaflex ava may be taken for a maximum of 16 treatment periods 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.

The recommended starting dose of adaflex ava tablets, independent of age, is 0.5-2 mg once a day, 30-60 minutes before the desired bedtime.

The dose of melatonin can be gradually increased every week until sufficient effect has been attained. The lowest effective dose should be sought. The maximum dose should not exceed 5 mg.

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 adaflex ava 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 moderately older adults in general, no specific dosage recommendations for elderly persons are provided (see sections 4.4 and 5.2). Caution should be exercised in treatment of significantly older patients and individual dosage is recommended.

Renal impairment
There is only limited experience regarding the use of melatonin in patients with renal impairment. Caution is recommended when melatonin is administered to this patient population. Melatonin is not recommended for patients with severe renal impairment (see section 5.2).

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

Impaired glucose tolerance
Intake of melatonin with carbohydrate-rich meals may impair blood glucose control for several hours (see Section 4.4).

Paediatric population
The efficacy and safety of melatonin for use in jet lag have not been established in children under 18 years.
The efficacy and safety of melatonin in children with ADHD aged 0-6 years have not been established.

Method of administration
Oral use.
The tablet can be crushed and dispersed in water directly before administration.

Food may enhance the increase in plasma melatonin concentration. It is recommended that food is not consumed 2 h before intake of adaflex ava and not 2 h after intake of adaflex ava (see section 5.2). Intake of melatonin with carbohydrate-rich meals may impair blood glucose control for several hours (see section 4.4).

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 tablets 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 tablets are 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.

Impaired glucose tolerance

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.

Excipients
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

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

CYP1A2 inhibitors
Concomitant treatment with melatonin and the CYP1A2 inhibitor fluvoxamine (also a CYP2C19 inhibitor) increased melatonin exposure 17-fold. The combination should be avoided.

Caution should be exercised when melatonin is used concomitantly with the following CYP1A2 inhibitors: ciprofloxacin, norfloxacin and verapamil.

Estrogen therapy: Estrogens increase melatonin level by inhibiting its metabolism, primarily via inhibition of CYP1A2. Coadministration of contraceptives containing ethinylestradiol and gestagen lead to a 4-5 times increase of the melatonin concentration. The dose of melatonin may need to be reduced.

Through interaction with moderately pronounced inhibitors of CYP1A2, increase of the plasma concentration of melatonin is expected. Caution is therefore indicated in patients taking 5- or 8-methoxypsoralen (5- or 8-MOP), cimetidine or caffeine.

CYP1A2 inhibitors (such as quinolones) may increase systemic melatonin levels.

CYP1A2 inducers
CYP1A2 inducers may decrease the plasma concentrations 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 (see section 4.2).

Nifedipine
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.

Benzodiazepine-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 insufficient with respect to reproductive toxicity (see section 5.3). Exogenous melatonin readily crosses the human placenta. Considering the lack of clinical data, treatment with adaflex ava is not recommended during pregnancy or in women of childbearing potential not using contraceptives.

Breastfeeding

Endogenous melatonin is secreted in human milk. Available pharmacodynamic / toxicological data in animals have shown excretion of exogenous melatonin / metabolites in milk (see section 5.3).
A risk to the breastfed child cannot be excluded. adaflex ava should not be used during breastfeeding.

Fertility
High doses of melatonin impaired male and female fertility in animals. The relevance of these data for human fertility is unknown.

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
Drowsiness/sleepiness, headache, and dizziness/disorientation are the most frequently reported adverse reactions when melatonin is taken on a short-term basis to treat jet lag and primary insomnia. Drowsiness, headache, dizziness, and nausea are also the adverse reactions reported most frequently when typical clinical doses of melatonin have been taken for periods of several days to several weeks by healthy persons and patients.

Tabulated list of adverse reactions
Adverse reactions in adults are listed according to MedDRA system organ class and presented within each frequency category according to the following: 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 estimated from the available data).

System organ class	**Very common**	**Common**	**Uncommon**	**Rare**	**Not known (cannot be estimated f the availab data)**
Infections and infestations				Herpes zoster	
Blood and lymphatic system disorders				Leukopenia, thrombocytopenia	
Immune system disorders					Hypersensit reaction
Metabolism and nutrition disorders				Hypertriglyceridemia, hypocalcaemia, hyponatraemia	Hyperglyca

System organ class	Very common	Common	Uncommon	Rare	Not known (cannot be estimated f the availab data)
Psychiatric disorders			Irritability, nervousness, restlessness, insomnia, abnormal dreams, nightmares, anxiety	Mood altered, aggression, agitation, crying, stress symptoms, disorientation, early morning awakening, libido increased, depressed mood, depression	Hallucinati
Nervous system disorders		Headache, somnolence	Migraine, lethargy, psychomotor hyperactivity, dizziness	Syncope, memory impairment, disturbance in attention, dreamy state, restless legs syndrome, poor quality sleep, paraesthesia	Drowsiness sedation
Eye disorders				Visual acuity reduced, vision blurred, lacrimation increased	
Ear and labyrinth disorders				Vertigo positional, vertigo	
Cardiac disorders				Angina pectoris, palpitations	
Vascular disorders			Hypertension	Hot flush	
Gastrointestinal disorders			Abdominal pain, abdominal pain upper, dyspepsia, mouth ulceration, dry mouth, nausea	Gastro-oesophageal reflux disease, gastrointestinal disorder, oral mucosal blistering, tongue ulceration, gastrointestinal upset, vomiting, bowel sounds abnormal, flatulence, salivary hypersecretion, halitosis, abdominal discomfort, gastric disorder, gastritis	
Hepatobiliary disorders			Hyperbilirubinemia		
Skin and			Dermatitis, night	Eczema, erythema,	Angioedem

System organ class	Very common	Common	Uncommon	Rare	Not known (cannot be estimated f the availab data)
subcutaneous tissue disorders			sweats, pruritus, rash, pruritus generalised, dry skin	hand dermatitis, psoriasis, rash generalised, rash pruritic, nail disorder	oedema of mouth, tong oedema
Musculoskeletal and connective tissue disorders			Pain in extremity	Arthritis, muscle spasms, neck pain, night cramps	
Renal and urinary disorders			Glycosuria, proteinuria	Polyuria, haematuria, nocturia	
Reproductive system and breast disorders			Menopausal symptoms	Priapism, prostatitis	Galactorrhc
General disorders and administration site conditions			Asthenia, chest pain	Fatigue, pain, thirst	
Investigations			Liver function test abnormal, weight increased	Hepatic enzyme increased, blood electrolytes abnormal, laboratory test abnormal	

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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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.

Doses of 250 mg taken 4 times daily during 25-30 days were 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 3000-6600 mg for 15-36 days, episodes of somnolence during daytime, abdominal cramps, diarrhoea, migraine headaches, cutaneous flushing or scotoma lucidum were reported.

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 02:00 hr and 04:00 hr 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 activity on MT1 and MT2 receptors is considered to contribute to its effect on sleep, as these receptors are involved in the regulation of 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 hr 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

Jet lag in adults
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 (between 22:00 hr and 24:00 hr), decreased jet lag from flights crossing six 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 mg 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 mg 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.

<u>Paediatric population</u>
Melatonin treatment has been studied in a 4-week randomised, double-blind, placebo-controlled study conducted in 105 children between 6-12 years of age, with ADHD and chronic sleep onset insomnia. 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.

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. There was a relatively large inter-individual variability observed in terms of the absolute bioavailability of melatonin. A generally low bioavailability could be attributed to the first-pass metabolism of melatonin.

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 mg 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 adaflex ava, however, it is recommended that food is not consumed approximately 2 h before and 2 h after intake of melatonin.

Distribution
The plasma protein binding of melatonin *in vitro* is about 60%. Distribution volume during terminal elimination phase is proportional to body weight, averaging just over 1 L/kg.

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 is comparable or slightly shorter in children (0.67 ± 0.12 h for prepubertal and 0.78 ± 0.11 h for pubertal) compared to adults (0.79 ± 0.10 h). Dosage once daily in combination with the short half-life means minimal accumulation of melatonin during regular treatment.

Linearity
Plasma melatonin C_{max} and AUC increase in a directly proportional, linear manner for oral doses of immediate-release melatonin in the range 1–10 mg, whereas T_{max} and plasma $t_{½}$ remain constant.

Gender
Limited data suggests that C_{max} 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. Dose adjustment for women is not necessary.

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
Decreased renal function is not expected to influence the elimination of melatonin as less than 1% of the dose is excreted unchanged in urine following an oral dose.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on studies of single and repeated dose toxicity, genotoxicity and carcinogenic potential. The data regarding reproductive toxicology is limited.

Embryo-fetal development studies in rats and rabbits did not show direct or indirect harmful effects with respect to pregnancy, fetal survival, fetal body weight, or incidences of fetal malformations/variations. Results from studies of prenatal and postnatal development in rats indicate that melatonin administration affects the hormonal level and sexual maturation in the offspring.

Data from animal studies indicate that melatonin is transmitted to the fetus via the placenta and to breast milk.

There are no safety studies in juvenile animals.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose (E 460)
Mannitol (E 421)
Silica, colloidal anhydrous (E 551)
Croscarmellose sodium (E 468)
Magnesium stearate (E 470b)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from light.

6.5 Nature and contents of container

HDPE bottle with polyethylene cap (tamper proof), containing 30 or 100 tablets.

HDPE bottle with polypropylene cap (tamper proof, child-resistant), containing 30 or 100 tablets.

Not all package sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

AGB-Pharma AB
Scheeletorget 1, Medicon Village
223 81 Lund
Sweden

8 MARKETING AUTHORISATION NUMBER(S)

PL 52497/0006

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

08/04/2026