SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Mellozzan 0.5 mg tablets
Mellozzan 1 mg tablets
Mellozzan 2 mg tablets
Mellozzan 3 mg tablets
Mellozzan 4 mg tablets
Mellozzan 5 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg, or 5 mg melatonin.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.
All strengths: White to yellowish, round biconvex tablet.
Mellozzan 0.5 mg: marked “0” on one side, tablet size, 7.5 mm diameter
Mellozzan 1 mg: marked “1” on one side, tablet size, 9.5 mm diameter
Mellozzan 2 mg: marked “2” on one side, tablet size, 7.0 mm diameter
Mellozzan 3 mg: marked “3” on one side, tablet size, 8.0 mm diameter
Mellozzan 4 mg: marked “4” on one side, tablet size, 9.0 mm diameter
Mellozzan 5 mg: marked “5” on one side, tablet size, 10.0 mm diameter

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Mellozzan is indicated for 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

Treatment should be initiated by physicians experienced in ADHD and/or treatment of paediatric sleep disorders.

Recommended starting dose of Mellozzan tablet: 0.5 - 2 mg 30 - 60 minutes before bedtime.

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

Limited data are available for up to 3 months of treatment and there is very limited data beyond that. In any case, the physician should assess the treatment effect at regular intervals and consider discontinuing

treatment if a clinically significant treatment effect has not been achieved. The patient should be monitored at regular intervals to check that Mellozzan is still the most appropriate treatment. During ongoing treatment, especially if the treatment effect is uncertain, attempts at discontinuation should be made regularly.

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

Children below 6 years of age
Mellozzan is not recommended for children under 6 years with ADHD. The safety and efficacy of melatonin in children less than 6 years has not been established.

Special populations

Renal impairment
No studies have been performed on the effect on melatonin pharmacokinetics at any stage of renal impairment. Caution should be exercised 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. Mellozzan is not recommended in patients with moderate or severe hepatic impairment (see section 5.2).

Method of administration
Oral use. The tablets may be crushed for administration and suspended in water.

Food can increase 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).

4.3 Contraindications

Hypersensitivity to the active substances 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 safety risks.

Immunological diseases
Occasional case reports have described exacerbation of autoimmune disease in patients taking melatonin. There are no data regarding use of melatonin 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. Due to the uncertainty of the effect of melatonin on epileptic seizures, 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 a meal by persons with significantly impaired glucose tolerance or diabetes.

Unnecessary long-term use of melatonin should be avoided due to its effects on glucose metabolism and increased risk for type 2 diabetes.

Risk of bleeding
Caution is advised when using melatonin together with anticoagulant drugs, including warfarin and novel direct-acting anticoagulants, as melatonin may enhance the effect of these drugs resulting in increased risk of bleeding (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions
Melatonin is primarily metabolized via CYP1A enzymes. Interactions between melatonin and other active substances affecting CYP1A enzymes are therefore possible.

CYP1A2 inhibitors
CYP1A2 inhibitor fluvoxamine considerably increased the melatonin plasma concentration (17-fold higher AUC and 12-fold higher C_{max}). Concomitant treatment with melatonin and the CYP1A2 inhibitor fluvoxamine (also a CYP2C19 inhibitor) should be avoided. Caution should be exercised when melatonin is used concomitantly with CYP1A2 inhibitors, such as ciprofloxacin.

Estrogens have been shown to increase melatonin concentrations by inhibiting CYP1A1 and CYP1A2 (a 4 - 5-fold increase in melatonin concentration during simultaneous use with combined hormonal contraception). Caution should be exercised in patients treated with estrogens (e.g., combined hormonal contraception or hormone replacement therapy).

Caffeine is a CYP1A2 substrate. Caffeine has been shown to increase serum concentrations of orally administered melatonin (2.2 times higher AUC and 2.4 times higher C_{max}).

Caution must be exercised in patients treated with 5- or 8-methoxypsoralen (5- or 8-MOP), which increases melatonin levels by inhibiting the metabolism of melatonin.

Caution should be exercised in patients who take cimetidine, as this product increases plasma melatonin levels by inhibiting its metabolism by CYP1A.

CYP1A2 inducers
CYP1A2 inducers may decrease the plasma concentrations of melatonin.

Dose adjustment of melatonin may be required in concomitant treatment with the following CYP1A2 inducers: carbamazepine, phenytoin, rifampicin, omeprazole and cigarette smoking (halved exposure compared with 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 pineal gland, 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 this combination may reduce the effect of melatonin on sleep.

Nifedipine
Melatonin may reduce the hypotensive effect of nifedipine. Caution must be exercised during concomitant use with melatonin and dose adjustment of nifedipine 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.

Anticoagulants

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 and fibrinogen. The combination of warfarin and direct-acting anticoagulants (e.g. dabigatran, rivaroxaban, apixaban, edoxaban) with melatonin may require dose adjustment of the anticoagulant products and should be avoided.

Benzodiazepine-like hypnotics
Melatonin may enhance the sedative effect of benzodiazepines (e.g. midazolam, temazepam) and non-benzodiazepine hypnotics (e.g. zaleplon, zolpidem, zopiclone). The use of melatonin in combination with these drugs is not recommended.

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.

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

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

4.6 Fertility, pregnancy and lactation

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

Breast-feeding
Data from animal studies indicate maternal transfer of melatonin to the fetus via the placenta or in 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 breast-feeding women.

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 a moderate influence on the ability to drive and use machines. Melatonin may cause drowsiness and should therefore be used with caution if drowsiness is 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 headaches, nausea and fatigue in both adults and children. However, these adverse reactions are also common for placebo-treated patients in reported clinical studies and no significant difference between patients receiving active substance and placebo is generally present in these studies.

No very common side effects have been reported.

Adverse reactions in adults are listed according to MedDRA system organ class and presented within each frequency category according to decreasing severity, with use of the following categories: 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).

System Organ Class	**Very common**	**Common**	**Uncommon**	**Rare**	**Not known**
Infections and infestations				Herpes zoster	
Blood and lymphatic system disorders				Leukopenia, thrombocytopenia	
Immune system disorders					Hypersensitivity reaction
Metabolism and nutrition disorders				Hypertriglyceridemia, hypocalcaemia, hyponatremia	Hyperglycaemia
Psychiatric disorders			Irritability, nervousness, restlessness, insomnia, abnormal dreams, nightmares, anxiety	Altered mood, aggression, agitation, crying, stress symptoms, disorientation, early morning awakening, libido increased, depressed mood, depression	
Nervous system disorders		Headache, somnolence	Migraine, lethargy, psychomotor hyperactivity, dizziness	Syncope, memory impairment, disturbance in attention, dreamy state, restless legs syndrome, poor quality sleep, paresthesia	
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 flushes	

Gastrointestinal disorders			Abdominal pain, upper abdominal pain, dyspepsia, mouth ulceration, dry mouth, nausea	Gastroesophageal 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 subcutaneous tissue disorders			Dermatitis, night sweats, pruritus, rash, pruritus generalized, dry skin	Eczema, erythema, hand dermatitis, psoriasis, rash generalized, rash pruritic, nail disorders	Angioedema, oedema oral, oedema tongue
Musculoskeletal and connective tissue disorders			Pain in the extremities	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	Galactorrhoea
General disorders and administration site conditions			Asthenia, chest pain	Fatigue, pain, thirst	
Investigations			Liver function test abnormal, weight increase	Hepatic enzyme increased, blood electrolytes abnormal, laboratory test abnormal	

Paediatric population
A low frequency of generally mild adverse reactions has 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. Long term effects are poorly studied (see section 5.1).

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 up to 300 mg for up to 2 years, without any clinically significant adverse reactions, have been reported in the literature.

One dose of 250 mg taken 4 times daily for 25 - 30 days has 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 naturally occurring hormone produced by the pineal gland and which is structurally related to serotonin. Melatonin secretion increases shortly after dark, reaching its peak between 2 am and 4 am and decreasing 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
The activity of melatonin on the MT1, MT2, and MT3 receptors is considered to contribute to its sleep-inducing properties, as these receptors (especially MT1 and MT2) 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 advance or delay, respectively, the circadian rhythmicity of melatonin secretion.

Clinical efficacy and safety in the 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 the diagnoses ADHD and chronic sleep onset insomnia (van der Heijden KB et al 2007). The 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 showed an improvement of 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 a sleep assessment scale for difficulty falling asleep decreased by 1.2 ± 1.2 points (35.3 % from baseline) with melatonin and by 0.1 ± 0.8 points (4.3 % from baseline) with placebo ($p < 0.0001$).

No significant effect on behaviour, cognition or life quality was observed.

No individual paused or interrupted treatment due to adverse effects.

There is very little long-term safety data on immediate-release melatonin products specifically in children and adolescents with ADHD.

5.2 Pharmacokinetic properties

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

Data on the pharmacokinetic effect of the intake of food, at or around the time of intake of melatonin, are limited, but suggest that concomitant food intake may increase 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 melatonin.

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

Melatonin primarily binds to albumin, though also binds alpha1-acid glycoprotein; binding to other plasma proteins is limited. Melatonin rapidly distributes from the plasma into and out of most tissues and organs, and readily crosses the brain-blood barrier.

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, around 90 % as sulphate and glucuronide conjugates of 6-hydroxymelatonin. Less than 1 % of a melatonin dose is excreted unchanged in urine.

Elimination
The plasma elimination half-life (T½) is approx. 45 minutes (normal range around 30 - 60 minutes) in healthy adults. The half-life, on average, is comparable or slightly shorter in children than in adults.

Linearity
Plasma melatonin C_{max} and AUC increase in a proportional, linear manner for oral doses of immediate-release melatonin in the dose range 0.25 – 10 mg.

Gender
Higher exposure and maximum plasma concentrations have been reported in women than men who received melatonin orally, however a significant variability in pharmacokinetics has been observed. Melatonin's plasma half-life does not appear to significantly differ between men and women. No dose adjustment is required for women.

Special patient groups

Hepatic impairment
Limited data indicate that the daytime endogenous blood melatonin concentration is markedly elevated in patients with liver cirrhosis, probably due to the reduced clearance (metabolism) of melatonin. Serum t½ 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 conducted on the effect on melatonin pharmacokinetics at any stage of renal impairment, see under section 4.2 Special populations.

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.

There are no safety studies on juvenile animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Pregelatinized starch (E 1404)
Microcrystalline cellulose (E 460)
Colloidal anhydrous silica (E 551)
Magnesium stearate (E 470b)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
0.5 mg and 1 mg: 2 years
2 mg, 3 mg, 4 mg, and 5 mg: 3 years

6.4 Special precautions for storage

Store in the original container in order to protect from light.

6.5 Nature and contents of container

HDPE bottle with polyethylene cap (tamper evident), containing 26, 30, 60 or 100 tablets.
Aluminium blister packs with 30 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

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

28-NOV-2025