SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Melatonin Vitabalans 1 mg tablets
Melatonin Vitabalans 2 mg tablets
Melatonin Vitabalans 4 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 mg tablets: Each tablet contains 1 mg melatonin.
2 mg tablets: Each tablet contains 2 mg melatonin.
4 mg tablets: Each tablet contains 4 mg melatonin.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

1 mg tablets: white to beige, capsule-shaped tablet. Dimensions of the tablet are 5 mm x 10 mm.
2 mg tablets: white to beige, round, convex tablet. Diameter of the tablet is 6 mm.
4 mg tablets: white to beige, round, convex tablet. Diameter of the tablet is 7 mm.
The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

{Invented name} is indicated for short-term treatment of jet lag in adults.

4.2 Posology and method of administration

Posology

Bioavailability differs between individuals, which is why the dosage should be individualized. The lowest effective dose should be sought.

The recommended dose is 1-5 mg daily. The dose should be taken at the time of bedtime at the destination when traveling over at least 5 time zones, especially when traveling in an easterly direction. The product can be also used if necessary, by travellers traveling over 2-4 time zones.
Melatonin should be used in jet lag for a maximum of 5 days.

Paediatric population

<invented name> is not recommended for children or adolescents under 18 years of age for the indication jet lag.

Special populations

Elderly

As the pharmacokinetics of exogenous 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 degree of renal impairment on the pharmacokinetics of melatonin has not been studied. Caution should be exercised if melatonin is used by patients with renal impairment. {Invented name} is not recommended for patients with severe renal impairment (see sections 4.4 and 5.2).

Hepatic impairment
There is no experience regarding the use of melatonin in patients with liver impairment. Published data show markedly elevated endogenous melatonin levels in patients with hepatic impairment. {Invented name} is not recommended for patients with hepatic impairment (see sections 4.4 and 5.2).

Method of administration

Oral use. Tablets should be swallowed with a glass of water.

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

The timing of the melatonin dosing is important. {Invented name} should be used as instructed.

Epilepsy
Caution should be exercised for use in people with epilepsy as melatonin has been reported to increase as well as decrease seizure frequency.

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

Autoimmune diseases
No clinical data exist concerning the use of melatonin in individuals with autoimmune diseases. Therefore, {Invented name} is not recommended for use in patients with autoimmune diseases.

Hepatic and renal impairment
There is only limited experience of safety and efficacy regarding the use of melatonin in patients with liver or kidney impairment. {Invented name} is not recommended for patients with hepatic impairment or severe renal impairment (see sections 4.4 and 5.2).

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 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

Interaction studies have only been performed in adults.

Pharmacokinetic interactions

CYP1A2 inhibitors

CYP1A2 inhibitors can substantially increase melatonin plasma concentration. CYP1A2 inhibitor fluvoxamine considerably increased the melatonin plasma concentration (17-fold higher AUC and 12-fold higher C_{max}). Concomitant treatment with melatonin and CYP1A2 inhibitor fluvoxamine (inhibits also CYP2C19) should be avoided.

Caution should be exercised during simultaneous treatment with melatonin and the following CYP1A2 inhibitors: ciprofloxacin, norfloxacin and verapamil.

Combined hormonal contraceptives containing ethinylestradiol and progestogen can inhibit CYP1A2 and increase melatonin plasma concentration 4 to 5-fold. The dose of melatonin might need to be reduced.

Hormonal replacement therapy in postmenopausal women has been reported to delay T_{max} of melatonin without other effects on plasma concentration or rhythm of melatonin.

Interaction with moderately strong inhibitors of CYP1A2 is expected to result in an increase in plasma concentration of melatonin. Therefore, caution should be exercised in patients taking 5 or 8-methoxypsoralene (5- or 8-MOP), cimetidine, or caffeine.

CYP1A2 inducers
CYP1A2 inducers may decrease plasma concentrations of melatonin. Dose adjustment of melatonin may be required during concomitant treatment with the following CYP1A2 inducers: carbamazepine, phenytoin, rifampicin, omeprazole and cigarette smoking (halved exposure compared to after 7 days of abstinence from smoking).

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, so caution should be exercised in this combination 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.

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 and non-benzodiazepine hypnotics such as zaleplon, zolpidem and zopiclone. In a clinical study, there was clear evidence of a transient pharmacodynamic interaction between melatonin prolonged-release tablet and zolpidem one hour after concomitant dosing. Concomitant administration led to an increased reduction in attention, memory and coordination compared to zolpidem alone.

Thioridazine/Imipramine
Melatonin may enhance the feelings of drowsiness and inability to perform tasks when administered with thioridazine or imipramine.

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 or limited amount of data for the use of melatonin in pregnant women. Exogenous melatonin readily crosses the human placenta. Animal studies are insufficient with respect to reproductive toxicity. {Invented name} is not recommended during pregnancy or in women of childbearing potential not using contraception. (see section 5.3).

Breastfeeding
Endogenous melatonin is secreted in human milk.
There is insufficient information on the excretion of melatonin in human milk. A risk to the suckling child cannot be excluded. {Invented name} should not be used during breast-feeding.

Fertility
There is very limited clinical data about effects of melatonin on fertility. Animal studies have shown an effect on spermatogenesis at doses that are higher and longer lasting than human doses (see section 5.3).

4.7 Effects on ability to drive and use machines

{Invented name} has moderate influence on the ability to drive and use machines. {Invented name} may cause drowsiness and impair alertness for hours; therefore, the product should be used with caution if the effects of drowsiness are likely to be associated with a risk to safety.

4.8 Undesirable effects

Summary of the safety profile
In clinical trials evaluating melatonin, very few adverse reactions have been reported. Overall, there is insufficient data to assess the occurrence and frequency of adverse effects of short-term use melatonin. Potential adverse reactions are headache, nausea, loss of appetite, dizziness, daytime sleepiness, and disorientation in both adults and children.

When used for various sleep disorders melatonin has been reported to cause a spectrum of adverse effects. All adverse effects are uncommon or rare, or the incidence is unknown.

With each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1000 to <1/100); Rare (≥1/10000 to <1/1000); Very rare (<1/10000), Not known (cannot be estimated from the available data).

System Organ Class	**Uncommon**	**Rare**	**Not known**
Infections and infestations		Herpes zoster	
Blood and lymphatic system disorders		Leukopenia, thrombocytopenia	
Immune system disorders			Hypersensitivity reaction

Metabolism and nutrition disorder		Hypertriglyceridaemia, hypocalcaemia, hyponatremia	
Psychiatric disorders	Irritability, nervousness, restlessness, insomnia, abnormal dreams, nightmares, anxiety	Mood changes, aggression, agitation, crying, stress symptoms, disorientation, early morning awakening, increased libido, depressed mood, depression	
Nervous system disorders	Migraine, headache, lethargy, psychomotor hyperactivity, dizziness, somnolence	Syncope, impaired memory, disturbance in attention, dreamy state, restless legs syndrome, poor quality sleep, paraesthesia	
Eye disorders		Acuity reduced, vision blurred, increased lacrimation	
Ear and labyrinth disorders		Positional vertigo, vertigo	
Cardiac disorders		Angina pectoris, palpitations	
Vascular disorders	Hypertension	Hot flushes	
Gastrointestinal disorders	Abdominal pain, 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	Hyperbilirubinaemia		
Skin and subcutaneous tissue disorders	Dermatitis, night sweats, pruritus, rash, pruritus generalised, dry skin	Eczema, erythema, hand dermatitis, psoriasis, generalised rash, pruritic rash, nail disorder	Angioedema, oedema of mouth, tongue 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	Galactorrhoea
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	

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

Administration of daily doses of up to 300 mg of melatonin without causing clinicaly significant adverse reaction have been reported in the literature.

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

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 is structurally related to serotonin. Physiologically, melatonin secretion increases soon after the onset of darkness, peaks at 2-4 am and diminishes during the second half of the night. Melatonin is associated with the control of circadian rhythms and entrainment to the light-dark cycle. It is also associated with a hypnotic effect and increased propensity for sleep.

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

Rationale for use
When used according to the instructions, melatonin alleviates symptoms of jet lag.

5.2 Pharmacokinetic properties

Absorption
The absorption of orally ingested melatonin is complete in adults.

Bioavailability is in the order of 15% (range 9 to 33%) due to extensive first-pass metabolism of melatonin. The T_{max} occurs usually approximately 50 minutes (normal range 15 to 90 minutes) after administration.

Based on limited data with high inter-subject variability, food intake may increase exposure and maximum plasma concentration of melatonin, likely not to a clinically relevant extent.

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 is O-demethylation to N-acetyl-5-hydroxytryptamine mediated by CYP2C19. Melatonin metabolites are mainly eliminated by the urine, ~ 90% as sulphate and glucuronide conjugates of 6-hydroxymelatonin. Less than 1% of the melatonin dose is excreted unchanged in the urine.

Elimination
Metabolites are excreted renally, 80% as 6-sulphatoxy-melatonin.

The elimination half life (t½) is approximately 45 minutes (range 30-60 minutes).

Linearity
The kinetics of oral melatonin are linear over range 0.25-10 mg.

Gender
Higher exposure and maximum plasma concentrations have been reported in women compared to men who have received melatonin orally, however a large variability in the pharmacokinetics is observed.
Plasma half-life does not appear to be significantly different in men and women. Dose adjustment for women are not necessary.

Special populations

Elderly
A comparative study of serum melatonin with and without exogenous supplementation found lower concentrations in moderately older adults without treatment, while a tendency for higher concentrations was observed compared to healthy younger adults after treatment. The difference was not statistically significant; The same dosage can be recommended for moderately older people as for younger adults

Renal impairment
No studies have been conducted on the pharmacokinetics of melatonin in any type of renal impairment, see section 4.2 Special populations.
As melatonin is primarily excreted as metabolites in the urine, serum/plasma levels of melatonin metabolites can be expected increase in patients with more advanced renal impairment.

Hepatic impairment
The effect of hepatic impairment on the pharmacokinetics of melatonin administered has not been studied. Published data show elevated endogenous melatonin levels in patients with hepatic impairment. As the liver is the primary site of melatonin metabolism, hepatic impairment can be expected to result in increased exposure to exogenous melatonin.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on studies of single-dose toxicity, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction and development.

An effect on spermatogenesis has been observed in animal studies at doses that are higher and longer lasting than human doses. The clinical relevance of this is unknown. Furthermore, effects in nonclinical studies were

observed only after exposure considered to be significantly greater than the maximum levels to which humans are exposed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium hydrogen phosphate dihydrate
Microcrystalline cellulose
Magnesium stearate
Silica colloidal anhydrous
Starch pregelatinised

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

1 mg: 2 years in blister packs, 3 years in tablet container
2 mg: 3 years
4 mg: 3 years

6.4 Special precautions for storage

1 mg tablets in blister packs:
Store below 25°C.
Store in the original package in order to protect from light.

1 mg tablets in tablet container and 2 mg and 4 mg tablets in blister packs and in tablet container:
Store in the original package in order to protect from light.

6.5 Nature and contents of container

10, 30 and 50 tablets in blisters (PVC/Aluminium) packed into unit carton.
10, 30 and 50 tablets in tablet container (container HD-PE plastic and closure LD-PE plastic) packed into unit carton.

Not all pack 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

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

2025-01-22