SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Melatonin Aristo 2 mg prolonged-release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release tablet contains 2 mg melatonin.

Excipients with known effect:
Each tablet contains 76.0 mg lactose (as lactose monohydrate).
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release tablet.

White to off white, round shaped, biconvex tablets, plain on both sides with a diameter of approximately 8 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Melatonin is indicated as monotherapy for the short-term treatment of primary insomnia characterised by poor quality of sleep in patients who are aged 55 or over.

4.2 Posology and method of administration

Posology
The recommended dose is 2 mg once daily, 1-2 hours before bedtime and after food.
This dosage may be continued for up to thirteen weeks.

Paediatric population
The safety and efficacy of Melatonin in children aged 0 to 18 years has not yet been established.
Other pharmaceutical forms/strengths may be more appropriate for administration to this population.
Currently available data are described in section 5.1.

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 such patients.

Hepatic impairment
There is no experience of the use of Melatonin in patients with liver impairment. Published data demonstrates markedly elevated endogenous melatonin levels during daytime hours due to decreased clearance in patients with hepatic impairment. Therefore, Melatonin is not recommended for use in patients with hepatic impairment.

Method of administration
Oral use.
Tablets should be swallowed whole to maintain prolonged release properties. Crushing or chewing should not be used to facilitate swallowing.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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.

No clinical data exist concerning the use of Melatonin in individuals with autoimmune diseases. Therefore, Melatonin is not recommended for use in patients with autoimmune diseases.

Melatonin Aristo contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Pharmacokinetic interactions

- Melatonin has been observed to induce CYP3A in vitro at supra-therapeutic concentrations. The clinical relevance of the finding is unknown. If induction occurs, this can give rise to reduced plasma concentrations of concomitantly administered medicinal products.
- Melatonin does not induce CYP1A enzymes in vitro at supra-therapeutic concentrations. Therefore, interactions between melatonin and other active substances as a consequence of melatonin's effect on CYP1A enzymes are not likely to be significant.
- Melatonin's metabolism is mainly mediated by CYP1A enzymes. Therefore, interactions between melatonin and other active substances as a consequence of their effect on CYP1A enzymes is possible.
- Caution should be exercised in patients on fluvoxamine, which increases melatonin levels (by 17-fold higher AUC and a 12-fold higher serum Cmax) by inhibiting its metabolism by hepatic cytochrome P450 (CYP) isozymes CYP1A2 and CYP2C19. The combination should be avoided.
- Caution should be exercised in patients on 5- or 8-methoxypsoralen (5 and 8-MOP), which increases melatonin levels by inhibiting its metabolism.
- Caution should be exercised in patients on cimetidine a CYP2D inhibitor, which increases plasma melatonin levels, by inhibiting its metabolism.
- Cigarette smoking may decrease melatonin levels due to induction of CYP1A2.
- Caution should be exercised in patients on oestrogens (e.g. contraceptive or hormone replacement therapy), which increase melatonin levels by inhibiting its metabolism by CYP1A1 and CYP1A2.
- CYP1A2 inhibitors such as quinolones may give rise to increased melatonin exposure.
- CYP1A2 inducers such as carbamazepine and rifampicin may give rise to reduced plasma concentrations of melatonin.
- There is a large amount of data in the literature regarding the effect of adrenergic agonists/antagonists, opiate agonists/antagonists, antidepressant medicinal products, prostaglandin inhibitors, benzodiazepines, tryptophan and alcohol, on endogenous melatonin secretion. Whether or not these active substances interfere with the dynamic or kinetic effects of Melatonin or vice versa has not been studied.

Pharmacodynamic interactions

- Alcohol should not be taken with Melatonin, because it reduces the effectiveness of Melatonin on sleep.
- Melatonin may enhance the sedative properties of benzodiazepines and non-benzodiazepine hypnotics, such as zaleplon, zolpidem and zopiclone. In a clinical trial, there was clear evidence for a transitory pharmacodynamic interaction between Melatonin and zolpidem one hour following co-dosing. Concomitant administration resulted in increased impairment of attention, memory and co-ordination compared to zolpidem alone.
- 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 tranquility and

difficulty in performing tasks compared to imipramine alone, and increased feelings of “muzzy-headedness” compared to thioridazine alone.

4.6 Fertility, pregnancy and lactation

Pregnancy
For melatonin, no clinical data on exposed pregnancies are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3). In view of the lack of clinical data, use in pregnant women and by women intending to become pregnant is not recommended.

Breastfeeding
Endogenous melatonin was measured in human breast milk thus exogenous melatonin is probably secreted into human milk. There are data in animal models including rodents, sheep, bovine and primates that indicate maternal transfer of melatonin to the foetus via the placenta or in the milk.
Therefore, breast-feeding is not recommended in women under treatment with melatonin.

4.7 Effects on ability to drive and use machines

Melatonin has moderate influence on the ability to drive and use machines. 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.

4.8 Undesirable effects

Summary of the safety profile
In clinical trials (in which a total of 1,931 patients were taking Melatonin and 1,642 patients were taking placebo), 48.8% of patients receiving Melatonin reported an adverse reaction compared with 37.8% taking placebo. Comparing the rate of patients with adverse reactions per 100 patient weeks, the rate was higher for placebo than Melatonin (5.743– placebo vs. 3.013– Melatonin). The most common adverse reactions were headache, nasopharyngitis, back pain, and arthralgia, which were common, by MedDRA definition, in both the Melatonin and placebo treated groups.

Tabulated list of adverse reactions
The following adverse reactions were reported in clinical trials and from post-marketing spontaneous reporting. In clinical trials a total of 9.5% of patients receiving Melatonin reported an adverse reaction compared with 7.4% of patients taking placebo. Only those adverse reactions reported during clinical trials occurring in patients at an equivalent or greater rate than placebo have been included below.

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

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 (frequency 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				Hypertriglyceridaemia, hypocalcaemia, hyponatraemia	
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	
Nervous system disorders			Migraine, headache, lethargy, psychomotor hyperactivity, dizziness, somnolence	Syncope, memory impairment, disturbance in attention, dreamy state, restless legs syndrome, poor quality sleep, paraesthesia	
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			Hyperbilirubinaemia		
Skin and subcutaneous tissue disorders			Dermatitis, night sweats, pruritus, rash, pruritus generalised, dry skin	Eczema, erythema, hand dermatitis, psoriasis, rash generalised, rash pruritic, 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 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

Several cases of overdose have been reported post-marketing. Somnolence was the most reported adverse event. Most were mild to moderate in severity. Melatonin has been administered at 5 mg daily doses in clinical trials over 12 months without significantly changing the nature of the adverse reactions reported.

Administration of daily doses of up to 300 mg of melatonin without causing clinically significant adverse reactions 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: Psycholeptics, 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
Because of the role of melatonin in sleep and circadian rhythm regulation, and the age related decrease in endogenous melatonin production, melatonin may effectively improve sleep quality particularly in patients who are over 55 with primary insomnia.

Clinical efficacy and safety
In clinical trials, where patients suffering from primary insomnia received Melatonin 2 mg every evening for 3 weeks, benefits were shown in treated patients compared to placebo in sleep latency (as measured by objective and subjective means) and in subjective quality of sleep and daytime functioning (restorative sleep) with no impairment of vigilance during the day.

In a polysomnographic (PSG) study with a run-in of 2 weeks (single-blind with placebo treatment), followed by a treatment period of 3 weeks (double-blind, placebo-controlled, parallel group design) and a 3-week withdrawal period, sleep latency (SL) was shortened by 9 minutes compared to placebo. There were no modifications of sleep architecture and no effect on REM sleep duration by Melatonin. Modifications in diurnal functioning did not occur with Melatonin 2 mg.

In an outpatient study with 2 week run-in baseline period with placebo, a randomised, double blind, placebo controlled, parallel group treatment period of 3 weeks and 2 week withdrawal period with placebo, the rate of patients who showed a clinically significant improvement in both quality of sleep and morning alertness was 47% in the Melatonin group as compared to 27% in the placebo group. In addition, quality of sleep and morning alertness significantly improved with Melatonin compared to placebo. Sleep variables gradually returned to baseline with no rebound, no increase in adverse reactions and no increase in withdrawal symptoms.

In a second outpatient study with two week run in baseline period with placebo and a randomised, double blind, placebo controlled, parallel group treatment period of 3 weeks, the rate of patients who showed a clinically significant improvement in both quality of sleep and morning alertness was 26% in the Melatonin group as compared to 15% in the placebo group. Melatonin shortened patients' reported sleep latency by

24.3 minutes vs 12.9 minutes with placebo. In addition, patients' self-reported quality of sleep, number of awakenings and morning alertness significantly improved with Melatonin compared to placebo. Quality of life was improved significantly with Melatonin 2 mg compared to placebo.

An additional randomised clinical trial (n=600) compared the effects of Melatonin and placebo for up to six months. Patients were re-randomised at 3 weeks. The study demonstrated improvements in sleep latency, quality of sleep and morning alertness, with no withdrawal symptoms and rebound insomnia. The study showed that the benefit observed after 3 weeks is maintained for up to 3 months but failed the primary analysis set at 6 months. At 3 months, about an extra 10% of responders were seen in the Melatonin treated group.

Paediatric population
A paediatric study (n=125) with doses of 2, 5 or 10 mg prolonged-release melatonin in multiples of 1 mg minitablets (age-appropriate pharmaceutical form), with two week run in baseline period on placebo and a randomised, double blind, placebo controlled, parallel group treatment period of 13 weeks, demonstrated an improvement in total sleep time (TST) after 13 weeks of double-blind treatment; participants slept more with active treatment (508 minutes), compared to placebo (488 minutes).

There was also a reduction in sleep latency with active treatment (61 minutes) compared to placebo (77 minutes) after 13 weeks of double-blind treatment, without causing earlier wake-up time.

In addition, there were fewer dropouts in the active treatment group (9 patients; 15.0%) compared to the placebo group (21 patients; 32.3%). Treatment emergent adverse events were reported by 85% patients in the active group and by 77% in the placebo group. Nervous system disorders were more common in the active group with 42% patients, compared to 23% in the placebo group, mainly driven by somnolence and headache more frequent in the active group.

5.2 Pharmacokinetic properties

Absorption
The absorption of orally ingested melatonin is complete in adults and may be decreased by up to 50% in the elderly. The kinetics of melatonin are linear over the range of 2-8 mg.

Bioavailability is in the order of 15%. There is a significant first pass effect with an estimated first pass metabolism of 85%. T_{max} occurs after 3 hours in a fed state. The rate of melatonin absorption and C_{max} following Melatonin 2 mg oral administration is affected by food. The presence of food delayed the absorption of the melatonin resulting in a later (T_{max}=3.0 h versus T_{max}=0.75 h) and lower peak plasma concentration in the fed state (C_{max}=1020 pg/ml versus C_{max}=1176 pg/ml).

Distribution
The in vitro plasma protein binding of melatonin is approximately 60%. Melatonin is mainly bound to albumin, alpha1-acid glycoprotein and high density lipoprotein.

Biotransformation
Experimental data suggest that isoenzymes CYP1A1, CYP1A2 and possibly CYP2C19 of the cytochrome P450 system are involved in melatonin metabolism. The principal metabolite is 6-sulphatoxy-melatonin (6-S-MT), which is inactive. The site of biotransformation is the liver. The excretion of the metabolite is completed within 12 hours after ingestion.

Elimination
Terminal half life (t½) is 3.5-4 hours. Elimination is by renal excretion of metabolites, 89% as sulphated and glucuronide conjugates of 6-hydroxymelatonin and 2% is excreted as melatonin (unchanged active substance).

Gender
A 3-4-fold increase in C_{max} is apparent for women compared to men. A five-fold variability in C_{max} between different members of the same sex has also been observed. However, no pharmacodynamic differences between males and females were found despite differences in blood levels.

Special populations

Elderly patients
Melatonin metabolism is known to decline with age. Across a range of doses, higher AUC and C_{max} levels have been reported in older patients compared to younger patients, reflecting the lower metabolism of melatonin in the elderly. C_{max} levels around 500 pg/ml in adults (18-45) versus 1200 pg/ml in elderly (55-69); AUC levels around 3,000 pg*h/mL in adults versus 5,000 pg*h/mL in the elderly.

Renal impairment
Company data indicates that there is no accumulation of melatonin after repeated dosing. This finding is compatible with the short half-life of melatonin in humans. The levels assessed in the blood of the patients at 23:00 (2 hours after administration) following 1 and 3 weeks of daily administration were 411.4 ± 56.5 and 432.00 ± 83.2 pg/ml respectively, and are similar to those found in in healthy volunteers following a single dose of Melatonin 2 mg.

Hepatic impairment
The liver is the primary site of melatonin metabolism and therefore, hepatic impairment results in higher endogenous melatonin levels.
Plasma melatonin levels in patients with cirrhosis were significantly increased during daylight hours. Patients had a significantly decreased total excretion of 6-sulfatoxymelatonin compared with controls.

5.3 Preclinical safety data

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

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

The carcinogenicity study in the rat did not reveal any effect which may be relevant for humans.

In reproductive toxicology, oral administration of melatonin in pregnant female mice, rats or rabbits did not result in adverse effects on their offspring, measured in terms of foetal viability, skeletal and visceral abnormalities, sex ratio, birthweight and subsequent physical, functional and sexual development. A slight effect on post-natal growth and viability was found in rats only at very high doses, equivalent to approximately 2000 mg/day in humans.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ammonio methacrylate copolymer type B
Calcium hydrogen phosphate dihydrate
Lactose monohydrate
Silica, colloidal anhydrous
Talc
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

15 months

6.4 Special precautions for storage

Do not store above 30°C.
Store in the original package in order to protect from light.

6.5 Nature and contents of container

Opaque, white, Alu-PVC/PVdC blisters packed in cardboard boxes.
Pack sizes: 7, 20, 21 or 30 tablets.
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

Aristo Pharma GmbH
Wallenroder Strasse 8-10
13435 Berlin
Germany

8 MARKETING AUTHORISATION NUMBER(S)

PL 40546/0257

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05/09/2025

10 DATE OF REVISION OF THE TEXT

05/09/2025