PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

VIGISOM prolonged-release tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each **VIGISOM** prolonged-release tablet contains 2 mg melatonin.

Contains sugar: 80 mg lactose monohydrate per tablet.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Prolonged-release tablet.

White to off-white, round, biconvex tablets, with no imprint or break-line.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

VIGISOM is indicated for the short- term up to 13 weeks treatment of primary insomnia characterised by poor quality of sleep, in patients who are aged 55 years or over.

4.2 Posology and method of administration

Posology

The recommended dose in patients 55 years and older is 2 mg once daily, 1-2 hours before bedtime and after food. The dosage may be continued for up to thirteen weeks.

Efficacy in patients younger than 55 years has not been demonstrated.

Special populations

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 **VIGISOM** in patients with liver impairment. Data demonstrates markedly elevated endogenous melatonin levels during daytime hours due to decreased clearance in patients with hepatic impairment. Therefore, **VIGISOM** is not recommended for use in patients with hepatic impairment.

Paediatric population

VIGISOM is not recommended for use in children and adolescents below age 18 due to insufficient data on safety and efficacy.

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 melatonin or to any of the excipients (see section 6.1) of **VIGISOM**.
- Safety in pregnancy and lactation has not been established (see section 4.6).

4.4 Special warnings and precautions for use

VIGISOM 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 **VIGISOM** in individuals with autoimmune diseases. Therefore, **VIGISOM** is not recommended for use in patients with autoimmune diseases.

VIGISOM contains lactose which may have an effect on the glycaemic control of patients with diabetes mellitus. Patients with rare hereditary problems of galactose intolerance, e.g. galactosaemia the LAPP lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Pediatric population

The safety and efficacy of **VIGISOM** in children aged 0 to 18 years has not yet been established.

4.5 Interaction with other medicines and other forms of interaction

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 (see section 5.2).
- 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 are possible.

- Caution should be exercised in patients on fluvoxamine, which increases melatonin levels (17-fold higher AUC and a 12-fold higher serum C_{max}) by inhibiting its metabolism by hepatic cytochrome P450 (CYP) isoenzymes CYP1A2 and CYP2C19. The combination should be avoided (see section 5.2).
- 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 around 68 % 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 (see section 5.2).
- 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, antidepressants, prostaglandin inhibitors, benzodiazepines, tryptophan, and alcohol, on endogenous melatonin secretion. Whether or not these active substances interfere with the dynamic or kinetic effects of **VIGISOM** or vice versa has not been studied.
- All sedatives can be expected to have an additive effect.

Pharmacodynamic interactions

- Alcohol should not be taken with **VIGISOM**, because it reduces the effectiveness of **VIGISOM** on sleep.
- **VIGISOM** may enhance the sedative properties of benzodiazepines and non-benzodiazepine hypnotics, such as zaleplon, zolpidem and zopiclone.
- **VIGISOM** has been co-administered in studies with thioridazine and imipramine. No clinically significant pharmacokinetic interactions were found.

4.6 Fertility, pregnancy, and lactation

Pregnancy

VIGISOM should not be used during pregnancy and lactation. Safety in pregnancy and lactation has not been established. (see section 4.3).

Breastfeeding

Endogenous melatonin was measured in breast milk thus exogenous melatonin is probably secreted into human milk. Mothers on **VIGISOM** should not breastfeed their infants.

4.7 Effects on ability to drive and use machines

VIGISOM may cause somnolence or dizziness. Patients should not engage in hazardous activities (such as driving or operating machinery) after taking **VIGISOM.**

4.8 Undesirable effects

a. Summary of the safety profile

The most common adverse reactions were headache, nasopharyngitis, back pain, and arthralgia.

b. Tabulated summary of adverse reactions

The following adverse effects were reported in clinical trials and were defined as possibly, probably, or definitely related to treatment.

Frequencies are defined as:

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 established from the available data).

MedDRA system organ class	**Uncommon**	**Rare**	**Not known**
Infections and infestations		Herpes zoster	
Blood and lymphatic system disorders		Leukopenia Thrombo-cytopenia	
Immune system disorders			Hypersensitivity reaction
Metabolism and nutrition disorders		Hyper-triglyceridaemia, Hypocalcaemia, Hyponatraemia	
Psychiatric disorders	Irritability, nervousness, restlessness, insomnia, abnormal dreams,	Altered mood, aggression, agitation, crying, stress symptoms, disorientation, early morning	

MedDRA system organ class	Uncommon	Rare	Not known
	nightmares, anxiety	awakening, increased libido, 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		Reduced visual acuity, blurred vision, increased lacrimation	
Ear and labyrinth disorders		Positional vertigo, vertigo.	
Cardiac Disorders		Angina pectoris, palpitations	
Vascular disorders	Hypertension	Hot flush	

MedDRA system organ class	Uncommon	Rare	Not known
Gastro-intestinal disorders	Abdominal pain, upper abdominal pain, dyspepsia, constipation, mouth ulceration, dry mouth, nausea (1)	Gastro-oesophageal reflux disease, gastrointestinal disorder, oral mucosal blistering, tongue ulceration, gastrointestinal upset, vomiting, abnormal bowel sounds, flatulence, salivary hypersecretion, halitosis, abdominal discomfort, gastric disorder, gastritis	
Hepatobiliary disorders	Hyper bilirubinaemia		
Skin and subcutaneous tissue disorders	Dermatitis, night sweats, pruritus, rash, pruritus generalised, dry skin	Eczema, erythema, hand dermatitis, psoriasis, rash generalized pruritic rash, nail	

MedDRA system organ class	Uncommon	Rare	Not known
		disorder	
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, nonspecific reaction	Fatigue, pain, thirst	
Investigations	Liver function test abnormal, increased weight	Hepatic enzyme increased, blood electrolytes abnormal, laboratory test abnormal	

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine.

Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions & Quality Problem Reporting Form**", found online under SAHPRA's publications:

https://sahpra.org.za/wp-content/uploads/2020/01/6.04_ARF1_v5.1_27Jan2020.pdf

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. **VIGISOM** 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

Pharmacological classification: A 2.2 Sedatives, hypnotics.

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 melatonin 1 (MT1), melatonin 2 (MT2) and melatonin 3 (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.

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 is 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} = 1 020 pg/ml versus C_{max} = 1 176 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 ($t_{½}$) is 3,5 - 4 hours. Elimination is by renal excretion of metabolites, 89 % as sulphated and glucoronide conjugates of 6-hydroxymelatonin and 2 % is excreted as unchanged melatonin

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 gender has also been observed. However, no pharmacodynamic differences between males and females were found despite differences in blood levels.

Special populations

Elderly

Melatonin metabolism is known to decline with age. Across a range of doses, higher AUC and C_{max} levels have been reported in older subjects compared to younger subjects, reflecting the lower metabolism of melatonin in the elderly. C_{max} levels around 500 pg/ml in adults (18-45) versus 1 200 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

There is no accumulation after repeated dosing. This finding is compatible with the short half-life in humans. The levels assessed in the blood of patients with end stage renal disease on chronic haemodialysis, at 23:00 (2 hours after administration) following 1 and 3 weeks of daily administration were 411,4 ± 56,5 and 432,0 ± 83,2 pg/ml respectively, and are similar to those found 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ammonio methacrylate copolymer type B

Calcium hydrogen phosphate dehydrate

Lactose monohydrate,

Magnesium stearate,

Silica, colloidal anhydrous

Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C. Protect from light.

Keep in the carton until required for use.

6.5 Nature and contents of container

The tablets are packed in white opaque PVC/PVdC/aluminium blisters.

One blister strip containing 7, 20 or 21 or two blister strips containing 15 tablets each (30 tablets). The blisters are then packed in a cardboard carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

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

7 HOLDER OF CERTIFICATE OF REGISTRATION

Acino Pharma (Pty) Ltd

106 16th Road

Midrand

1686, South Africa

8 REGISTRATION NUMBER(S)

59/2.2/0054

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

31 October 2023

10 DATE OF REVISION OF THE TEXT

31 October 2023