PROFESSIONAL INFORMATION:

SCHEDULING STATUS:

S4

1. NAME OF THE MEDICINE:

CADIATEV (prolonged-release tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

CADIATEV contains melatonin 2 mg per prolonged-release tablet.

Excipient with known effect*:*

Contains sugar (lactose monohydrate 80 mg per tablet).

For the full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM:

Prolonged-release tablets.

White to off-white, oval, biconvex prolonged-release tablets with no scoring, marked ‘A6’ on one side.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications:

CADIATEV 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 to 2 hours before bedtime and after food. The dosage may be continued for up to 13 weeks.

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

Special Populations:

Renal impairment:

The effect of any stage of renal insufficiency 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 use of melatonin as contained in CADIATEV 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, CADIATEV is not recommended for use in patients with hepatic impairment.

Paediatric-population:

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

Method of administration:

For oral use. Tablets should be swallowed whole.

4.3 Contraindications:

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

4.4 Special warnings and precautions for use:

No clinical data exist concerning the use of CADIATEV in individuals with autoimmune diseases.

Therefore, CADIATEV is not recommended for use in patients with autoimmune diseases.

CADIATEV 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.

Paediatric population:

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

CADIATEV 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 medicines 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 medicines.
- 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 are possible.
- Caution should be exercised in patients on fluvoxamine, which increases melatonin levels (by 17-fold higher AUC and a 12-fold higher serum C_{max}) 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 medicines, 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 CADIATEV, because it reduces the effectiveness of CADIATEV on sleep.
- CADIATEV 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 CADIATEV and zolpidem one hour following co-dosing. Concomitant administration resulted in increased impairment of attention, memory and co-ordination compared to zolpidem alone.

- CADIATEV 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, CADIATEV 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.

4.6 Fertility, pregnancy and lactation:

Pregnancy:

Safety in pregnancy has not been established. There are no clinical data available on use in pregnancy.

Breastfeeding:

Safety in lactation has not been established.

Endogenous melatonin was measured in breast milk thus exogenous melatonin is probably secreted into human milk.

Fertility:

There are no data on fertility.

4.7 Effects on ability to drive and use machines:

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

System Organ Class MedDRA:	
Infections and infestations:	
Less frequent	Herpes Zoster
Blood and lymphatic disorders:	
Less frequent	Leukopenia, thrombocytopenia
Immune system disorders:	
Frequency unknown	Hypersensitivity reaction
Metabolism and nutrition disorders:	
Less frequent	Hypertriglyceridaemia, hypocalcaemia, hyponatraemia
Psychiatric disorders:	
Less frequent	Irritability, nervousness, restlessness, insomnia, abnormal dreams, nightmares, anxiety, altered mood, aggression, agitation, crying, early morning awakening, increased libido, disorientation, depressed mood, depression
Nervous system disorders:	
Less frequent	Migraine, psychomotor hyperactivity, dizziness, lethargy, somnolence, memory impairment, disturbance in attention, poor quality sleep, headache, syncope, memory impairment, paraesthesia, restless legs syndrome
Eye disorders:	
Less frequent	Reduced visual acuity, blurred vision, increased lacrimation
Ear and labyrinth disorders:	
Less frequent	Positional vertigo, vertigo
Cardiac disorders:	
Less frequent	Angina pectoris, palpitations

Vascular disorders:	
Less frequent	Hot flush, hypertension
Gastrointestinal disorders:	
Less frequent	Abdominal pain, constipation, abdominal pain upper, dyspepsia, dry mouth, gastrointestinal disorder, gastrointestinal upset, vomiting, abnormal bowel sounds, flatulence, salivary hypersecretion, halitosis, mouth ulceration, nausea, gastro-oesophageal reflux disease, oral mucosal blistering, tongue ulceration, vomiting, abdominal discomfort, gastric disorder, gastritis
Hepato-biliary disorders:	
Less frequent	Hyperbilirubinaemia, hepatic enzyme increased, liver function test abnormal, laboratory test abnormal
Skin and subcutaneous tissue disorders:	
Less frequent	Dermatitis, hyperhidrosis, eczema, erythema, pruritic rash, pruritus, dry skin, nail disorder, night sweats, hand dermatitis, psoriasis, rash generalised
Frequency unknown	Angioedema, oedema of mouth, tongue oedema
Renal and urinary disorders:	
Less frequent	Glycosuria, proteinuria, polyuria, haematuria, nocturia
Musculoskeletal and connective tissue disorders:	
Less frequent	Pain in extremity, muscle cramp, neck pain, arthritis, night cramps
Reproductive system and breast disorders:	
Less frequent	Menopausal symptoms, priapism, prostatitis
Frequency unknown	Galactorrhoea
General disorders and administration site conditions:	
Less frequent	Asthenia, chest pain, fatigue, pain, thirst
Investigations:	

Less frequent	Increased weight, blood electrolytes 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. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the **6.04 Adverse Drug Reactions Reporting Form**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

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. CADIATEV 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:

A 2.2 Sedatives, hypnotics

Pharmacotherapeutic group: Psycholeptics, melatonin receptor agonists, ATC code: N05CH01

Mechanism of Action:

Melatonin is a 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 to 4 am and diminished 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.

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 to 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 CADIATEV 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 to 4 hours. Elimination is by renal excretion of metabolites, 89 % as sulphated and glucuronide conjugates of 6-hydroxymelatonin and 2 % is excreted as unchanged melatonin.

Gender:

A 3- to 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. 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 lower metabolism of melatonin in the elderly. C_{max} levels around 500 pg/ml in adults (18 to 45) versus 1200 pg/ml in the elderly (55 to 69); AUC levels around 3000 pg/h/ml in adults versus 5000 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 hemodialysis, 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 (200 Mesh)

Magnesium stearate

Silica, colloidal anhydrous

Talc

6.2 Incompatibilities:

Not applicable.

6.3 Shelf life:

Blisters (PVC/PE/PVdC/PE/PVC/Al): 18 months

Blisters (PVC/PVdC/Al): 24 months

HDPE containers: 24 months

6.4 Special precautions for storage:

Blisters packs: Store at or below 25 °C. Store in the original package in order to protect from light.

HDPE containers: Store at or below 30 °C. Store in the original package in order to protect from light.

6.5 Nature and contents of container:

Blister packs (PVC/PVdC/Al or PVC/PE/PVdC/PE/PVC/Al) of 20, 21, 30 or 90 prolonged-release tablets in an outer cardboard carton.

Plastic (HDPE) containers closed with a sealed plastic cap (PP-closure), with desiccant integrated in the cap, containing 100 prolonged release-tablets.

Not all pack sizes will be marketed.

6.6 Special precautions for disposal and handling:

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

7. HOLDER OF THE CERTIFICATE OF REGISTRATION:

Teva Pharmaceuticals (Pty) Ltd.

Maxwell Office Park

Magwa Crescent West

Waterfall City

Midrand

Gauteng

South Africa

2090

8. REGISTRATION NUMBERS:

56/2.2/0389

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION:

30 May 2023

10. DATE OF REVISION OF THE TEXT:

30 October 2024