

**Applicant:** Aurogen South Africa (Pty) LTD  
**Product Name:** Medploz 5mg and 10mg.  
**Dosage form and strength:**  
Each film coated tablet contains  
Zolpidem tartarate 10mg and 5mg.



**Amended: 16 January 2023**

## APPROVED PROFESSIONAL INFORMATION

**SCHEDULING STATUS:** S5

### PROPRIETARY NAME (and dosage form):

**MEDPLOZ 5 mg** (Tablet)

**MEDPLOZ 10 mg** (Tablet)

### COMPOSITION:

**MEDPLOZ 5 mg:** Each film-coated tablet contains 5 mg zolpidem tartrate. Contains lactose.

**MEDPLOZ 10 mg:** Each film-coated tablet contains 10 mg zolpidem tartrate. Contains lactose.

### PHARMACOLOGICAL CLASSIFICATION:

A.2.2 Sedatives, hypnotics.

### PHARMACOLOGICAL ACTION:

Zolpidem is an imidazopyridine compound with sedative/hypnotic effects. These effects are related to a specific agonist action at central receptors belonging to GABA-omega benzodiazepine-1 and benzodiazepine-2 macromolecular receptor complex, modulating the opening of the chloride ion channel. Zolpidem acts primarily upon the omega-1 (benzodiazepine-1) receptor subtypes. The clinical relevance of this is not known.

### Pharmacokinetics:

#### Absorption:

The bioavailability of Zolpidem is about 70 % after oral administration. Peak plasma concentration is reached between 0,5 and 3 hours after dosing.

#### Distribution:

The pharmacokinetics are linear at therapeutic dose levels. The degree of plasma protein binding is about 92 %. The plasma elimination half-life is about 2,5 hours (1,4 – 3,8 hours).

The distribution volume in adults is  $0,54 \pm 0,02$  l/kg. The distribution volume decreases to  $0,34 \pm 0,05$  l/kg in the very elderly.

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**Excretion:**

Zolpidem is excreted in the form of inactive metabolites (hepatic metabolism), mainly in the urine (56 %) and faeces (37 %). It has no inducing effects on hepatic enzymes. Clearance is reduced in elderly subjects. The peak concentration is increased by about 50 % and elimination half-life by 32 %. In patients with renal insufficiency, whether dialysed or not, there is a moderate reduction in clearance. The other pharmacokinetic parameters are unaffected.

**Bioavailability:**

In patients with hepatic insufficiency, the bioavailability of zolpidem is increased. Clearance is reduced and the elimination half-life prolonged (about 10 hours).

**INDICATIONS:**

**MEDPLOZ** is indicated for the short term treatment of insomnia.

**MEDPLOZ**, is only indicated when the disorder is severe, disabling or subjecting the individual to extreme distress.

**CONTRA-INDICATIONS:**

Hypersensitivity to the product.

Myasthenia gravis.

Sleep apnoea syndrome.

Acute and severe pulmonary insufficiency, as respiratory failure may be precipitated.

Severe hepatic insufficiency.

Children under the age of 18.

Concomitant administration with HIV protease inhibitors such as ritonavir as plasma concentrations may be increased and thus the risk of extreme sedation and respiratory depression.

**WARNINGS AND SPECIAL PRECAUTIONS:**

Safety and efficacy in children under the age of 18 years have not been established.

Dependence and Abuse:

Use of **MEDPLOZ** may lead to the development of physical and psychological dependence. The risk of dependence increases with the dose and duration of treatment; it is also greater in patients with a

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history of alcohol or medicine abuse. These patients should be under careful surveillance when receiving hypnotics. Discontinuation of therapy may result in withdrawal or rebound phenomena.

**Duration of treatment:**

The duration of treatment should be as short as possible and should not exceed 4 weeks, including the tapering off process. Extensions beyond these periods should not take place without re-evaluation of the situation.

It may be useful to inform the patient when treatment is started that it will be of limited duration, and to explain precisely how the dosage will be progressively decreased.

**Tolerance:**

After repeated use of **MEDPLOZ** for a few weeks, some loss of efficacy of the hypnotic effects may develop.

Depression: **MEDPLOZ** should not be used to treat depressive syndromes, or anxiety with depression as suicidal tendencies may be present.

Psychotic illness: **MEDPLOZ** should not be used as the primary treatment of psychotic illness.

History of alcohol and drug abuse: **MEDPLOZ** should not be used in patients with a history of alcohol or drug abuse.

**Amnesia:**

**MEDPLOZ** may induce anterograde amnesia. The condition occurs most often several hours after ingesting the product and therefore, to reduce this risk, patients should ensure that they will be able to have an uninterrupted sleep of 7 to 8 hours (see **Side – effects**).

**Rebound Insomnia:**

A transient syndrome, whereby the symptoms that led to treatment with sedative/ hypnotic agents recur in an enhanced form, may occur on withdrawal of hypnotic treatment. It may be accompanied by other reactions including mood changes, anxiety and restlessness. The syndrome is more likely to develop if the product is discontinued abruptly, and therefore treatment should be withdrawn gradually.

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### **Psychiatric and “Paradoxical” Reactions:**

See **Side – effects**.

### **Dependence and Abuse:**

Use of **MEDPLOZ** may lead to the development of physical and psychological dependence. The risk of dependence increases with the dose and duration of treatment; it is also greater in patients with a history of alcohol or medicine abuse. These patients should be under careful surveillance when receiving hypnotics.

Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms. These may consist of headaches or muscle pain, extreme anxiety and tension, restlessness, confusion and irritability. In severe cases, the following symptoms may occur: derealisation, depersonalisation, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures.

**MEDPLOZ** may produce withdrawal signs and symptoms following abrupt discontinuation. These symptoms range from mild dysphoria and insomnia to a withdrawal syndrome that may include abdominal and muscle cramps, vomiting, sweating, tremors and convulsions.

### **Specific patient groups:**

- For the elderly: See dose recommendations.
- Respiratory insufficiency: Since hypnotics have been shown to impair respiratory drive, caution should be observed when prescribing **MEDPLOZ** to patients with chronic respiratory insufficiency.
- Severe hepatic insufficiency: Zolpidem is not indicated to treat patients with severe hepatic insufficiency as hypnotics may precipitate encephalopathy.

### **Effects on ability to drive or to use machines:**

Sedation, drowsiness, dizziness and vertigo may adversely affect the ability to drive or to use machines in patients taking **MEDPLOZ**. The likelihood of impaired alertness may increase if insufficient sleep duration occurs.

### **INTERACTIONS:**

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- Concomitant intake with alcohol is not recommended. The sedative effect may be enhanced when the product is used in combination with alcohol. This affects the ability to use machines or drive.
- Combination with CNS depressants: Enhancement of the central depressive effects may occur in cases of concomitant use with antipsychotics (neuroleptics), hypnotics, anxiolytics/sedatives, antidepressant agents, narcotic analgesics, antiepileptic medicines, anaesthetics and sedative antihistamines.

In the case of narcotic analgesics enhancement of the euphoria may also occur leading to an increase in psychological dependence.

- The activity of **MEDPLOZ** may be enhanced by compounds which inhibit certain hepatic enzymes (particularly cytochrome P450). Zolpidem is metabolised via several hepatic cytochrome P450 enzymes: the main enzyme being CYP3A4 with the contribution of CYP1A2. The pharmacodynamic effect of **MEDPLOZ** is decreased when it is administered with rifampicin (a CYP3A4 inducer).

However when zolpidem was administered with itraconazole (a CYP3A4 inhibitor) its pharmacokinetics and pharmacodynamics were not significantly modified. The clinical relevance of these results is unknown.

- No significant pharmacokinetic interactions were observed when **MEDPLOZ** was administered with warfarin, digoxin or ranitidine.
- HIV-protease inhibitors such as ritonavir may increase plasma concentrations of zolpidem with a risk of profound sedation and respiratory depression; use together is not recommended.

#### **PREGNANCY AND LACTATION:**

Safety in pregnancy has not been established.

If **MEDPLOZ** is administered during the late phase of pregnancy, or during labour, effects on the neonate such as hypothermia, hypotonia and moderate respiratory depression, can be expected due to the pharmacological action of the product.

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Infants born to mothers who take **[PRODUCT NAME ]** chronically during the latter stages of pregnancy may develop physical dependence and may be at some risk of developing withdrawal symptoms in the postnatal period.

Zolpidem should not be administered to breast-feeding mothers.

Small quantities of zolpidem appear in breast milk.

## **DOSAGE AND DIRECTIONS FOR USE**

**Safety and efficacy in children under the age of 18 years have not been established.**

Treatment should be as short as possible. Generally, the duration of treatment varies from a few days to two weeks with a maximum, including the tapering off process, of four weeks.

In certain cases, extension beyond the maximum treatment period may be necessary. If so, it should not take place without re-evaluation of the patient's status.

**MEDPLOZ** should be taken immediately before going to bed, or in bed.

### **Dose:**

**The recommended daily dose for adults is 10 mg immediately before bedtime, or in bed.**

In elderly or debilitated patients who may be especially sensitive to the effects of zolpidem, and in patients with hepatic insufficiency who do not clear the agent as rapidly as normal individuals, a dose of 5 mg is recommended, which should be exceeded only under exceptional circumstances. The total dose of **MEDPLOZ** should not exceed 10 mg in any patient.

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## **SIDE-EFFECTS:**

### **Nervous system disorders:**

Less frequent: Drowsiness during the day, confusion, headache, dizziness, ataxia and gait disturbances.

Amnesia: Anterograde amnesia may occur using therapeutic dosages of **MEDPLOZ**, the risk increasing at higher dosages. Amnesic effects may be associated with inappropriate behaviour.

The following side effects have been reported and frequencies are unknown: Reduced alertness, fatigue.

### **Psychiatric disorders:**

Less frequent: Depression: Pre-existing depression may be unmasked during the use of **MEDPLOZ**.

Psychiatric and "Paradoxical" reactions: Reactions like restlessness, agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects are known to occur when using [**PRODUCT NAME**]. Should this occur, use of the product should be discontinued. These reactions are more likely to occur in children (see **Contra-indications**) and in the elderly.

The following side effect has been reported and frequency is unknown: Numbed emotions.

### **Musculoskeletal, connective tissue and bone disorders:**

Less frequent: Muscle weakness.

### **Eye disorders:**

Less frequent: Double vision.

These phenomena mentioned above occur predominantly at the start of therapy and most frequently in elderly patients, but may disappear with repeated administration.

### **Gastrointestinal disorders:**

Less frequent: Gastro-intestinal disturbances, such as nausea, vomiting, diarrhoea, dry mouth, abdominal or gastric pain.

### **Skin and subcutaneous tissue disorders:**

Less frequent: Skin reactions.

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#### **KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:**

Following an overdose with **MEDPLOZ** alone, impairment of consciousness may range from somnolence to light coma. Individuals have fully recovered from zolpidem doses of up to 400 mg. Overdose involving multiple CNS-depressant agents (e.g. alcohol), may result in more severe symptomatology, including fatal outcomes.

#### **Treatment:**

General symptomatic and supportive measures should be used, along with immediate gastric lavage where appropriate. Intravenous fluids should be administered as needed. Sedative medicines should be withheld even if excitation occurs. The value of dialysis in the treatment of overdose has not been determined, although haemodialysis studies in patients with renal failure receiving therapeutic doses have demonstrated that zolpidem is not dialysable. Where serious symptoms are observed, the use of benzodiazepine – antagonists (e.g. flumazenil) may be considered.

However, flumazenil administration may contribute to the appearance of neurological symptoms (convulsions).

In the management of overdose with any medicinal product, it should be borne in mind that multiple agents may have been taken.

#### **IDENTIFICATION:**

**MEDPLOZ 5 mg:** White to off – white, circular, biconvex, film – coated tablets, debossed with “E” on one side and “78” on the other side.

**MEDPLOZ 10 mg:** White to off – white, oval shaped, biconvex film – coated tablets, debossed with “E” on one side and debossed with “80” with a score line between “8” and “0” on the other side.

#### **PRESENTATION:**

**MEDPLOZ 5 mg, MEDPLOZ 10 mg:**

##### **1. Blister Packs:**

Tablets are packed in blister packs composed of clear PVC / PVdC and printed silver-coloured aluminium foil. Each blister contains 10 tablets.

Pack size: 30's – Each carton contains 3 blisters of 10 tablets each.

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## **Medploz 10 mg**

### **2. Blister Packs:**

Tablets are packed in blister packs composed comprises of clear PVC / PVdc and printed silver-coloured aluminium foil. Each blister contains 14 tablets.

**Pack size: 14s** - Each carton contains 1 blister of 14 tablets each.

### **2. HDPE Container Pack:**

Tablets are packed in white opaque HDPE containers with white opaque polypropylene closure with induction sealing wad. The void space in the container is filled by Rayon coil.

Pack size: 30's: One HDPE container of 30 tablets

### **STORAGE INSTRUCTIONS:**

Store in a dry place at or below 25 °C. Protect from light and moisture. Keep blisters in the original carton until required for use. Keep the HDPE container well closed.

KEEP OUT OF REACH OF CHILDREN.

### **REGISTRATION NUMBER:**

**MEDPLOZ 5 mg:** 43/2.2/0247

**MEDPLOZ 10 mg:** 43/2.2/0257

### **NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF**

#### **REGISTRATION:**

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