## 1.3 Product Information

### 1.3.1 Summary of Product Characteristics (SmPC)

**1. Name of the medicinal product**

ZOPICLONE TABLETS BP 7.5 MG

**2. Qualitative and quantitative composition**

| SR. NO. | NAME OF THE INGREDIENTS | PHARMACOPEIAL SPECIFICATION | LABLE CLAIM | OVERAGES % | QTY. / TABLET | PURPOSE |
|---|---|---|---|---|---|---|
| **ACTIVE INGREDIENTS** | | | | | | |
| 1. | Zopiclone* | BP | 7.50 mg | 2.00 % | 7.650 mg | API |
| **INACTIVE INGREDIENTS** | | | | | | |
| 2. | Anhydrous lactose | BP | - | 0.00 % | 24.800 mg | Diluent |
| 3. | Maize starch | BP | - | 0.00 % | 60.000 mg | Diluent |
| 4. | Microcrystalline cellulose | BP | - | 0.00 % | 40.000 mg | Diluent |
| 5. | Povidone | BP | - | 0.00 % | 4.500 mg | Binder |
| 6. | Isopropyl alcohol** | BP | - | 0.00 % | 0.050 ml | Solvent |
| 7. | Magnesium stearate | BP | - | 0.00 % | 2.000 mg | Lubricant |
| 8. | Purified talc | BP | - | 0.00 % | 3.000 mg | Glidant |
| 9. | Croscarmellose sodium | BP | - | 0.00 % | 6.000 mg | Disintegrant |
| 10. | Colloidal silicon dioxide | USP | - | 0.00 % | 2.000 mg | Glidant |
| 11. | Acetone** | BP | - | 0.00 % | 0.030 ml | Solvent |
| 12. | Isopropyl alcohol** | BP | - | 0.00 % | 0.020 ml | Solvent |
| 13. | Titanium dioxide | BP | - | 0.00 % | 0.050 mg | Colour |
| 14. | Hydroxypropylmethyl Cellulose E15 | BP | - | 0.00 % | 3.500 mg | Polymer |
| 15. | Purified talc | BP | - | 0.00 % | 0.250 mg | Glidant |
| 16. | Titanium dioxide | BP | - | 0.00 % | 0.250 mg | Opacifier |
| 17. | Polyethylene glycol (macrogol) 6000 | BP | - | 0.00 % | 1.000 mg | Plasticizer |

* 2.00 % overages are added on label claim to compensate loss during storage
**Evaporates during manufacturing & does not remain in final product.

**3. Pharmaceutical form**

Oral Tablet

**4. Clinical particulars**

**4.1 Therapeutic indications**

Zopiclone is indicated for the short term treatment of insomnia where sleep initiation or sleep maintenance are prominent symptoms. Long term use is not recommended as tolerance, dependence, addiction can occur with prolonged use.

**4.2 Posology and method of administration**

**Posology**
**Adults:** One tablet (7.5 mg zopiclone) orally, shortly before retiring. This dose should not be exceeded.
**Elderly patients and patients with impaired liver function or chronic respiratory insufficiency:** A lower dose of 3.75 mg zopiclone (half a tablet) should be employed to start treatment in these patients, and if necessary the dose may be increased to 7.5 mg.
**Method of administration**
For oral use.

**4.3 Contraindications**

Zopiclone is contra-indicated in patients with a hypersensitivity to zopiclone, myasthenia gravis, respiratory failure, severe sleep apnoea syndrome and severe hepatic insufficiency. Zopiclone should not be used in children under the age of 18.Safety in pregnancy and lactation has not been established

**4.4 Special warnings and precautions for use**

**Warnings:**
- Drowsiness and in co-ordination on waking can occur.
- Patients should be cautioned about driving motor vehicles or operating machinery until it has been established that their performance is not affected

**Precautions:**
- Hepatic and renal insufficiency; elderly; psychiatric disorders; history of drug abuse.
- May impair ability to drive or operate machinery.
- Limit treatment duration to <4 week to minimise risk of dependence and tolerance.
- Avoid abrupt discontinuation of therapy.

**4.5 Interaction with other medicinal products and other forms of interaction**

Zopiclone also interacts with trimipramine and caffeine. Alcohol has an additive effect when combined with zopiclone, enhancing the adverse effects including the overdose potential of zopiclone significantly A study assessing the impact of zopiclone on driving skills the next day found that the impairments on driving skills are double that of a social dose of alcohol. Zaleplon had no detrimental effects on driving skills the next day. Carbamazepine also has additive effects when combined with zopiclone with both drugs enhancing the side effects of each other. Erythromycin appears to increase the absorption rate of zopiclone and prolong the elimination half-life of zopiclone leading to increased plasma levels and more pronounced effects. Itraconazole has a similar effect on zopiclone pharmacokinetics as erythromycin. The elderly may be particularly sensitive to the erythromycin and itraconazole drug interaction with zopiclone. Temporary dosage reduction during combined therapy may be required especially in the elderly. Rifampicin causes a very notable reduction in half-life of zopiclone and peak plasma levels which results in a large

reduction in the hypnotic effect of zopiclone. Phenytoin and carbamazepine may also provoke similar interactions. Ketoconazole and sulfaphenazole interfere with the metabolism of zopiclone. Nefazodone impairs the metabolism of zopiclone leading to increased zopiclone levels and marked next day sedation

### 4.6 Pregnancy and lactation

Insufficient data are available on zopiclone to assess its safety during human pregnancy and lactation.

**Pregnancy:**

Experience of use of zopiclone during pregnancy in humans is limited although there have been no adverse findings in animals. Use in pregnancy is therefore not recommended.

If the product is prescribed to a woman of child bearing potential, she should be advised to contact her physician about stopping the product if she intends to become pregnant, or suspects that she is pregnant.

Moreover, if zopiclone is used during the last three months of pregnancy or during labour, due to the pharmacological action of the product, effects on the neonate, such as hypothermia, hypotonia and respiratory depression can be expected.

Infants born to mothers who took benzodiazepines or benzodiazepine- like agents chronically during the latter stages of pregnancy may have developed physical dependence and may be at some risk of developing withdrawal symptoms in postnatal period.

**Breast-feeding:**

Zopiclone is excreted in breast milk and, although the concentration of Zopiclone in the breast milk is low, use in nursing mothers must be avoided.

### 4.7 Effects on ability to drive and use machines

Because of its pharmacological properties and its effect on central nervous system, Zopiclone may adversely affect the ability to drive or to use machines. The risk of psychomotor impairment, including impaired driving ability, is increased if:

- Zopiclone is taken within 12 hours of performing activities that require mental alertness,
- A dose higher than the recommended dose is taken, or
- Zopiclone is co-administered with other cns depressants, alcohol, or with other drugs that increase the blood levels of zopiclone.

Patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness or motor coordination such as operating machinery or driving a motor vehicle following administration of zopiclone and in particular during the 12 hours following that administration.

### 4.8 Undesirable effects

The side effect most commonly seen in clinical trials is taste alteration or dysgeusia (bitter, metallic taste, which is usually fleeting in most users but can persist until the drug's half-life has expired). Palpitations may occur in the daytime following withdrawal from the drug after prolonged periods of use (especially when taken for more than two weeks).

Zopiclone induces amnesia type memory impairments similar to triazolam and Rohypnol. Impairment of driving skills with a resultant increased risk of road traffic accidents is probably the most important side effect. This side effect is not unique to zopiclone but also occurs with other hypnotic drugs

More common reactions
Gastrointestinal: taste disturbances including bitter metallic taste, dry mouth. Nervous system: disruption of REM sleep, double vision, drowsiness, memory impairments, visuospatial impairments, dizziness, headaches, and fatigue Unexpected mood changes have been noted, which if experienced should lead to the drug being withdrawn from the patient.
Less common reactions:

- **Gastrointestinal**: heartburn, constipation, diarrhoea, nausea, coated tongue, bad breath, anorexia or increased appetite, vomiting, epigastric pains, dyspepsia, dehydration, parageusia.
- **Cardiovascular**: palpitations in elderly patients.
- **Skin**: urticaria, tingling in the arms and legs.
- **Miscellaneous**: blurred vision, frequent micturition, mild to moderate increases in serum transaminases and/or alkaline phosphatase and interstitial nephritis have been reported very rarely.
- **Reproductive**: impotence, delayed ejaculation, anorgasmia in both women and men
- **Nervous system**: agitation anxiety, loss of memory including retrograde and anterograde amnesia, confusion, dizziness, weakness, somnolence, asthenia, euphoria and/or dysphoria, feeling of drunkenness, depression, sleep walking, coordination abnormality, hypotonia, speech disorder, hallucinations of various strengths, usually auditory and visual, behavioural disorders, aggression, tremor, rebound insomnia, nightmares, hypomania. Delirium can also occur but is a side effect mainly seen in the elderly.

### 4.9 Overdose

Fatal dose not known
**Symptoms:**
Overdose is usually manifested by varying degrees of central nervous system depression ranging from drowsiness to coma according to the quantity ingested. Overdose should not be life-threatening unless combine with the CNS depressants (including alcohol).
Symptomatic and supportive treatment in an adequate clinical environment is recommended; attention should be paid to respiratory
and cardiovascular functions. Gastric lavage is only useful when performed soon after ingestion. Haemodialysis is of no value due to the large volume of distribution of zopiclone. Flumazenil may be a useful antidote.

## 5. Pharmacological properties

### 5.1 Pharmacodynamic properties

**Pharmacotherapeutic group:** Cyclopyrrolone; Drugs used in insomnia. ATC Code: N05CF01
**Mechanism of action:** Zopiclone exerts its action by binding on the benzodiazepine receptor complex and modulation of the $GABA_BZ$ receptor chloride channel macromolecular complex. Both zopiclone and benzodiazepines act indiscriminately at the benzodiazepine binding site on α1, α2, α3 and α5 GABAA containing receptors as full agonists causing an enhancement of the inhibitory actions of GABA to produce the therapeutic (hypnotic and anxiolytic) and adverse effects of zopiclone.

### 5.2 Pharmacokinetic properties

After oral administration, zopiclone is rapidly absorbed, with a bioavailability of approximately 80%. The plasma protein binding of zopiclone has been reported to be between 45 and 80%. Zopiclone is rapidly and widely distributed to body tissues including the brain, and is excreted in urine, saliva and breast milk. Zopiclone is partly metabolised in the liver to form an inactive N-demethylated derivative and an active N-oxide metabolite. In addition, approximately 50% of the administered dose is decarboxylated and excreted via the lungs. In urine, the N-demethyl and N-oxide metabolites account for 30% of the initial dose. Between 7 and 10% of zopiclone is recovered from the urine indicating extensive metabolism of the drug before excretion. The terminal elimination half-life (t1/2z) of zopiclone ranges from 3.5 to 6.5 hours. The pharmacokinetics of zopiclone in humans are stereoselective. After oral administration of the racemic mixture, Cmax (time to maximum plasma concentration), AUC (area under the plasma time-concentration curve) and t1/2z values are higher for the dextrorotatory enantiomer owing to the slower total clearance and smaller volume of distribution (corrected by the bioavailability), compared with the levorotatory enantiomer. In urine, the concentrations of the dextrorotatory enantiomers of the N-demethyl and N-oxide metabolites are higher than those of the respective antipodes. The pharmacokinetics of zopiclone are altered by aging and are influenced by renal and hepatic functions

### 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, and toxicity to reproduction and development

## 6. Pharmaceutical particulars

### 6.1 List of Excipients

- Anhydrous lactose
- Maize starch
- Microcrystalline cellulose
- Povidone
- Isopropyl alcohol
- Magnesium stearate
- Purified talc
- Cross carmellose sodium
- Colloidal silicon dioxide
- Acetone
- Titanium dioxide
- Hydroxypropylmethylcellulose E15
- Polyethylene glycol (macrogol) 6000

### 6.2 Incompatibilities

Not applicable

### 6.3 Shelf life

48 months.

**6.4 Special precautions for storage**

Store in a dry place at a temperature below 30°C.

**6.5 Nature and contents of container**

20 × 1 × 10 tablets Alu-PVC blister pack, packed in printed and laminated carton.

**6.6 Special precautions for disposal and other handling**

Not applicable.

**7. Marketing authorisation holder**

West Coast Pharmaceutical Works Ltd, Ahmedabad

**8. Marketing authorisation number(s)**

Not applicable.

**9. Date of first authorisation/renewal of the authorisation**

Not applicable.

**10. Date of revision of the text**

May, 2018