# Summary of Product Characteristics

## 1. Name of the Medicinal Product

**Zopimac 2/3** (Eszopiclone Tablets USP 2/3 mg)

## 2. Qualitative and Quantitative Composition

Each film coated Tablet Contains:
Eszopiclone USP ...2/3 mg

*For full excipients list see point 6.1*

## 3. Pharmaceutical Form

Tablet
**Description:**
**Zopimac 2** (Eszopiclone Tablets USP 2 mg):
White, round, biconvex, film coated tablet, debossed with “L 35” on one side and plain onthe other side.

**Zopimac 3** (Eszopiclone Tablets USP 3 mg):
White, round, biconvex, film coated tablet, debossed with “L 36” on one side and plain onthe other side.

## 4. Clinical Particulars

### 4.1. Therapeutic indications

Eszopiclone is indicated for the treatment of insomnia.

### 4.2. Posology and method of administration

Use the lowest effective dose for the patient.

**Dosage in Adults:**
The recommended starting dose is 1 mg. Dosing can be raised to 2 mg or 3 mg if clinically indicated. In some patients, the higher morning blood levels of Eszopiclone following use of the 2 mg or 3 mg dose increase the risk of next day impairment of driving and other activities that require full alertness. The total dose of Eszopiclone should not exceed 3 mg, once daily immediately before bedtime.

**Geriatric or Debilitated Patients:**
The total dose of Eszopiclone should not exceed 2 mg in elderly or debilitated patients.

**Patients with Severe Hepatic Impairment, or Taking Potent CYP3A4 Inhibitors:**
In patients with severe hepatic impairment, or in patients co-administered Eszopiclone with potent CYP3A4 inhibitors, the total dose of Eszopiclone should not exceed 2 mg.

**Use with CNS Depressants:**
Dosage adjustments may be necessary when Eszopiclone is combined with other CNS depressant drugs because of the potentially additive effects.

**Administration with Food:**
Taking Eszopiclone with or immediately after a heavy, high-fat meal results in slower absorption and would be expected toreduce the effect of Eszopiclone on sleep latency.

**4.3. Contraindications**.
It is contraindicated in patients with known hypersensitivity to eszopiclone. Hypersensitivity reactions include anaphylaxis and angioedema.

**4.4. Special warnings and precautions for use**
**CNS Depressant Effects and Next-Day Impairment:**
Eszopiclone is a central nervous system (CNS) depressant and can impair daytime function in somepatients at the higher doses (2 mg or 3 mg), even when used as prescribed. Prescribers should monitor for excess depressant effects, but impairment can occur in the absence of symptoms (or even with subjective improvement), and impairment may not be reliably detected by ordinary clinical exam (i.e., less than formal psychomotor testing). While pharmacodynamic tolerance or adaptation to some adverse depressant effects of Eszopiclone may develop, patients using 3 mgEszopiclone should be cautioned against driving or engaging in other hazardous activities or activities requiring complete mental alertness the day after use.

Additive effects occur with concomitant use of other CNS depressants (e.g., benzodiazepines, opioids, tricyclic antidepressants, alcohol), including daytime use. Downward dose adjustment of Eszopiclone and concomitant CNS depressants should be considered.

The use of Eszopiclone with other sedative-hypnotics at bedtime or the middle of the night is not recommended.

The risk of next-day psychomotor impairment is increased if Eszopiclone is takenwith less than a full night of sleep remaining (7-to 8 hours); if higher than the recommended dose is taken; if co-administered with other CNS depressants; or co-administered with other drugs that increase the blood levels of eszopiclone.

**Need to Evaluate for Co-Morbid Diagnoses:**
Because sleep disturbances may be the presenting manifestation of a physical and/or psychiatric disorder,

symptomatic treatment of insomnia should be initiated only after a careful evaluation of the patient. The failure of insomnia to remit after 7 to 10 days of treatment may indicate the presence of a primary psychiatric and/or medical illness that should be evaluated. Worsening of insomnia or the emergence of new thinking or behavior abnormalities may be the consequence of an unrecognized psychiatric or physical disorder. Such findings have emerged during the course of treatment with sedative/hypnotic drugs, including Eszopiclone. Because some of the important adverse effects of Eszopiclone appear to be dose-related, it is important to use the lowest possible effective dose, especially in the elderly.

**Severe Anaphylactic and Anaphylactoid Reactions:**
Rare cases of angioedema involving the tongue, glottis or larynx have been reported in patients after taking the first or subsequent doses of sedative-hypnotics, including Eszopiclone. Some patients have had additional symptoms such as dyspnea, throat closing, or nausea and vomiting that suggest anaphylaxis. Some patients have required medical therapy in the emergency department. If angioedema involves the tongue, glottis or larynx, airway obstruction may occur and be fatal. Patients who develop angioedema after treatment with Eszopiclone should not be re-challenged with the drug.

**Abnormal Thinking and Behavioral Changes:**
A variety of abnormal thinking and behavior changes have been reported to occur in association with the use of sedative/hypnotics. Some of these changes may be characterized by decreased inhibition (e.g., aggressiveness and extroversion that seem out of character), similar to effects produced by alcohol and other CNS depressants. Other reported behavioral changes have included bizarre behavior, agitation, hallucinations, and depersonalization. Amnesia and other neuropsychiatric symptoms may occur unpredictably. In primarily depressed patients, worsening of depression, including suicidal thoughts and actions (including completed suicides), has been reported in association with the use of sedative/hypnotics.

Complex behaviors such as “sleep-driving” (i.e., driving while not fully awake after ingestion of a sedative-hypnotic, with amnesia for the event) have been reported. These events can occur in sedative-hypnotic-naïve as well as in sedative-hypnotic-experienced persons. Although behaviors such as sleep-drivingmay occur with Eszopiclone alone at therapeutic doses, the use of alcohol and other CNS depressants with Eszopiclone appears to increase the risk of such behaviors, as does the use of Eszopiclone at doses exceeding the maximumrecommended dose. Due to the risk to the patient and the community, discontinuation of Eszopiclone should be strongly considered for patients who report a “sleep-driving” episode. Other complex behaviors (e.g., preparing and eating food, making phone calls, or having sex) have been reported in patients who are not fully awake after taking a sedative-hypnotic. As with sleep-driving, patients usually do not remember these events.

It can Rarely be determined with certainty whether a particular instance of the abnormal behaviors listed above are drug-induced, spontaneous in origin, or a result of an underlying psychiatric or physical disorder. Nonetheless, the emergence of any new behavioral sign or symptom of concern requires careful and immediate evaluation.

**Withdrawal Effects:**
Following rapid dose decrease or abrupt discontinuation of the use of sedative/ hypnotics, there have been reports of signs and symptoms similar to those associated with withdrawal from other CNS-depressant drugs.

**Timing of Drug Administration:**
Eszopiclone should be taken immediately before bedtime. Taking a sedative/ hypnotic while still up and about may result in short-term memory impairment, hallucinations, impaired coordination, dizziness, and lightheadedness.

**Special Populations**
**Use in Elderly and/or Debilitated Patients**:
Impaired motor and/or cognitive performance after repeated exposure or unusual sensitivity to sedative/hypnotic drugs is a concern in the treatment of elderly and/ or debilitated patients. The dose should not exceed 2 mg in elderly or debilitated patients.

**Use in Patients with Concomitant Illness:**
Clinical experience with eszopiclone in patients with concomitant illness is limited. Eszopiclone should be used with caution in patients with diseases or conditions that could affect metabolism or hemodynamic responses. Caution is advised, however, if Eszopiclone is prescribed to patients with compromised respiratory function.

The dose of Eszopiclone should not exceed 2 mg in patients with severe hepatic impairment, because systemic exposure is doubled in such subjects. No dose adjustment appears necessary for subjects with mild or moderate hepatic impairment. No dose adjustment appears necessary in subjects with any degree of renal impairment, since less than 10% of eszopiclone is excreted unchanged inthe urine.

The dose of Eszopiclone should be reduced in patients who are administered potent inhibitors of CYP3A4, such as ketoconazole, while taking Eszopiclone. Downward dose adjustment is also recommended when Eszopiclone is administered with agents having known CNS-depressant effects.

**Use in Patients with Depression:**
Sedative/hypnotic drugs should be administered with caution to patients exhibiting signs and symptoms of depression. Suicidal tendencies may be present in such patients, and protective measures may be required. Intentional overdose is more common in this group of patients; therefore, the least amount of drug that is feasible should be prescribed for the patient at any one time.

**Lactose Monohydrate:**
This product contains Lactose Monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose galactose malabsorption should not take this medicine.

**Macrogol:** This product contains Macrogol it may cause stomach upset and diarrhea.

**4.5. Interaction with other medicinal products and other forms of interaction**
**CNS Active Drugs**
Ethanol: An additive effect on psychomotor performance was seen with co-administration of eszopiclone and ethanol.
Olanzapine: Co-administration of eszopiclone and olanzapine produced a decreasein DSST scores. The interaction was pharmacodynamic; there was no alterationin the pharmacokinetics of either drug.

**Drugs that Inhibit or Induce CYP3A4:**
Drugs That Inhibit CYP3A4 (Ketoconazole) - CYP3A4 is a major metabolic pathway for elimination of eszopiclone. The exposure of eszopiclone was increased by co-administration of ketoconazole, a potent inhibitor of CYP3A4. Other strong inhibitors of CYP3A4 (e.g., itraconazole, clarithromycin, nefazodone, troleandomycin, ritonavir, nelfinavir) would be expected to behave similarly. Dose reduction of eszopiclone is needed for patient co-administered eszopiclone with potent CYP3A4 inhibitors.

Drugs that Induce CYP3A4 (Rifampicin) - Racemic zopiclone exposure was similar effect would be expected with eszopiclone. Combination use with CYP3A4 inducer may decrease the exposure and effects of eszopiclone.

**Drug Abuse and Dependence**

Controlled Substance: Eszopiclone is a Schedule IV controlled substance under the Controlled Substances Act. While eszopiclone is a hypnotic agent with a chemical structure unrelated to benzodiazepines, it shares some of the pharmacologic properties of the benzodiazepines.

Abuse: In a study of abuse liability conducted in individuals with known histories of benzodiazepine abuse, eszopiclone at doses of 6 and 12 mg produced euphoric effects similar to those of diazepam 20 mg. In this study, at doses 2-fold or greater than the maximum recommended doses, a dose-related increase in reportsof amnesia and hallucinations was observed for both eszopiclone and diazepam. Dependence: The clinical trial experience with eszopiclone revealed no evidence of a serious withdrawal syndrome. Nevertheless, the following adverse events included in DSM-IV criteria for uncomplicated sedative/hypnotic withdrawal were reported during clinical trials following placebo substitution occurring within 48 hours following the last eszopiclone treatment: anxiety, abnormal dreams, nausea, and upset stomach.

These reported adverse events occurred at an incidence of 2% or less. Use of benzodiazepines and similar agents may lead to physical and psychological dependence. The risk of abuse and dependence increases with the dose and duration of treatment and concomitant use of other psychoactive drugs. The risk is also greater for patients who have a history of alcohol or drug abuse or history of psychiatric disorders. These patients should be under careful surveillance when receiving eszopiclone or any other hypnotic.

Tolerance: Some loss of efficacy to the hypnotic effect of benzodiazepines and benzodiazepine-like agents may develop after repeated use of these drugs for a few weeks.

No development of tolerance to any parameter of sleep measurement was observed over six months. Tolerance to the efficacy of eszopiclone 3 mg was assessed by 4-week objective and 6-week subjective measurements of time to sleep onset and sleep maintenance for eszopiclone in a placebo-controlled 44-day study, and by subjective assessments of time to sleep onset and WASO in a placebo-controlled study for 6 months.

**4.6. Pregnancy and Lactation**

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. Eszopiclone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
It is not known whether this drug is excreted in human milk.

**4.7. Effects on ability to drive and use machines**

Patients using eszopiclone should be cautioned against driving or engaging in other hazardous activities or activities requiring complete mental alertness the day after use.

**4.8. Undesirable effects**

**Adverse Reactions Observed at an Incidence of ≥ 2%**
**Body as a Whole:** Headache, Viral Infection, Accidental Injury, Pain
**Digestive System:** Dry Mouth, Dyspepsia, Nausea, Vomiting, Diarrhea

**Nervous System:** Anxiety, Confusion, Depression, Dizziness, Hallucinations, Libido Decreased, Nervousness, Somnolence, Abnormal Dreams, Neuralgia

**Respiratory System:** Infection

**Skin and Appendages:** Rash, Pruritus
**Special Senses:** Unpleasant Taste
**Urogenital System:** Dysmenorrhea, Gynecomastia, Urinary Tract Infection

**Reactions are further categorized by body system and listed in order of decreasing frequency according to the following definitions:**
Frequent adverse reactions are those that occurred on one or more occasions in at least 1/100 patients; In frequent adverse reactions are those that occurred in fewerthan 1/100 patients but in at least 1/1,000 patients; Rare adverse reactions are those that occurred in fewer than 1/1,000 patients. Gender-specific reactions are categorized based on their incidence for the appropriate gender.

**Body as a Whole:**
Frequent: chest pain;
Infrequent: allergic reaction, cellulitis, face edema, fever, halitosis, heat stroke, hernia, malaise, neck rigidity, photosensitivity.

**Cardiovascular System:**
Frequent: migraine;
Infrequent: hypertension; Rare: thrombophlebitis.

**Digestive System:**
Infrequent: anorexia, cholelithiasis, increased appetite, melena, mouth ulceration,thirst, ulcerative stomatitis;
Rare: colitis, dysphagia, gastritis, hepatitis, hepatomegaly, liver damage, stomachulcer, stomatitis, tongue edema, rectal hemorrhage.

**Hemic and Lymphatic System:** In frequent: anemia, lymphadenopathy.
**Metabolic and Nutritional:**
Frequent: peripheral edema;
Infrequent: hypercholesteremia, weight gain, weight loss; Rare: dehydration,gout, hyperlipemia, hypokalemia.

**Musculoskeletal System:**
Infrequent: arthritis, bursitis, joint disorder (mainly swelling, stiffness, and pain), leg cramps, myasthenia, twitching;
Rare: arthrosis, myopathy, ptosis.

**Nervous System:**
Infrequent: agitation, apathy, ataxia, emotional lability, hostility, hypertonia, hypesthesia, incoordination, insomnia, memory impairment, neurosis, nystagmus, paresthesia, reflexes decreased, thinking abnormal (mainly difficulty concentrating), vertigo;
Rare: abnormal gait, euphoria, hyperesthesia, hypokinesia, neuritis, neuropathy,stupor, tremor.

**Respiratory System:** Infrequent: asthma, bronchitis, dyspnea, epistaxis, hiccup,laryngitis.

**Skin and Appendages:**
Infrequent: acne, alopecia, contact dermatitis, dry skin, eczema, skindiscoloration, sweating, urticaria;
Rare: erythema multiforme, furunculosis, herpes zoster, hirsutism, maculopapularrash, vesiculobullous rash.

**Special Senses:**
Infrequent: conjunctivitis, dry eyes, ear pain, otitis externa, otitis media, tinnitus, vestibular disorder;
Rare: hyperacusis, iritis, mydriasis, photophobia.

**Urogenital System:**
In frequent: amenorrhea, breast engorgement, breast enlargement, breast neoplasm, breast pain, cystitis, dysuria, female lactation, hematuria, kidney calculus, kidney pain, mastitis, menorrhagia, metrorrhagia, urinary frequency, urinary incontinence, uterine hemorrhage, vaginal hemorrhage, vaginitis;
Rare: oliguria, pyelonephritis, urethritis.

## 4.9. Overdose

Signs and Symptoms: Signs and symptoms of overdose effects of CNS depressants can be expected to present as exaggerations of the pharmacological effects noted in preclinical testing. Impairment of consciousness ranging from somnolence to coma has been described. Rare individual instances of fatal outcomes following overdose with racemic zopiclone have been reported in post marketing reports, most often associated with overdose with other CNS-depressant agents.

**Recommended Treatment:**
General symptomatic and supportive measures should be used along with immediate gastric lavage where appropriate. Intravenous fluids should be administered as needed. Flumazenil may be useful. As in all cases of drug overdose, respiration, pulse, blood pressure, and other appropriate signs should be monitored and general supportive measures employed. Hypotension and CNS depression should be monitored and treated by appropriate medical intervention. The value of dialysis in the treatment of overdosage has not been determined.

As with the management of all overdosage, the possibility of multiple drug ingestion should be considered.

# 5. Pharmacological Properties

## 5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Hypnotics and sedatives, benzodiazepine relateddrugs,
**ATC code:** N05CF04
The precise mechanism of action of eszopiclone as a hypnotic is unknown, but its effect is believed to result from its interaction with GABA-receptor complexes at binding domains located close to or allosterically coupled to benzodiazepine receptors. Eszopiclone is a non-benzodiazepine hypnotic that is a pyrrolopyrazine derivative of the cyclopyrrolone class with a chemical structure unrelated to pyrazolopyrimidines, imidazopyridines, benzodiazepines, barbiturates, or otherdrugs with known hypnotic properties.

## 5.2. Pharmacokinetic properties

### Absorption and Distribution

Eszopiclone is rapidly absorbed following oral administration. Peak plasma concentrations are achieved within approximately 1 hour after oral administration. Eszopiclone is weakly bound to plasma protein (52-59%). The large free fraction suggests that eszopiclone disposition should not be affected by drug-drug interactions caused by protein binding. The blood-to-plasma ratio for eszopiclone is less than one, indicating no selective uptake by red blood cells.

### Metabolism

Following oral administration, eszopiclone is extensively metabolized byoxidation and demethylation. The primary plasma metabolites are (S)-zopiclone- N-oxide and (S)-N-desmethyl zopiclone; the latter compound binds to GABA receptors with substantially lower potency than eszopiclone, and the former compound shows no significant binding to this receptor. In vitro studies have shown that CYP3A4 and CYP2E1 enzymes are involved in the metabolism of eszopiclone. Eszopiclone did not show any inhibitory potential on CYP450 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4 in cryopreserved human hepatocytes.

### Elimination

After oral administration, eszopiclone is eliminated with a mean t½ of approximately 6 hours. Up to 75% of an oral dose of racemic zopiclone is excreted in the urine, primarily as metabolites. A similar excretion profile would be expected for eszopiclone, the S-isomer of racemic zopiclone. Less than 10% of the orally administered eszopiclone dose is excreted in the urine as parent drug.

### Effect of Food

In healthy adults, administration of a 3 mg dose of eszopiclone after a high-fat meal resulted in no change in AUC, a reduction in mean Cmax of 21%, and delayed tmax by approximately 1 hour.

The half-life remained unchanged, approximately 6 hours. The effects of eszopiclone on sleep onset may be reduced if it is taken with or immediately aftera high-fat/heavy meal.

## 5.3. Preclinical safety data

In a carcinogenicity study in rats, oral administration of eszopiclone for 97 (males) or 104 (females) weeks resulted in no increases in tumors; plasma levels (AUC) of eszopiclone at the highest dose tested (16 mg/kg/day) are approximately 80 (females) and 20 (males) times those in humans at the maximum recommended human dose (MRHD) of 3 mg/day. However, in a 2-year carcinogenicity study in rats, oral administration of racemic zopiclone (1, 10, or 100 mg/kg/day) resulted in increases in mammary gland adenocarcinomas (females) and thyroid gland follicular cell adenomas and carcinomas (males) at the highest dose tested.

Plasma levels of eszopiclone at this dose are approximately 150 (females) and 70 (males) times those in humans at the MRHD of eszopiclone. The mechanism for the increase in mammary adenocarcinomas is unknown. The increase in thyroid tumors is thought to be due to increased levels of TSH secondary to increased metabolism of circulating thyroid hormones, a mechanism not considered relevant to humans.

In a 2-year carcinogenicity study in mice, oral administration of racemic zopiclone (1, 10, or 100 mg/kg/day) produced increases in pulmonary carcinomas and carcinomas plus adenomas (females) and skin fibromas and sarcomas (males) at the highest dose tested. The skin tumors were due to skin lesions induced by aggressive behavior, a mechanism not relevant to humans.

A carcinogenicity study of eszopiclone was conducted in mice at oral doses up to 100 mg/kg/day. Although this study did not reach a maximum tolerated dose, and was thus inadequate for overall assessment of carcinogenic potential, no increases in either pulmonary or skin tumors were seen at doses producing plasma levels of eszopiclone approximately 90 times those in humans at the MRHD ofeszopiclone (and 12 times the exposure in the racemate study).

Eszopiclone did not increase tumors in a p53 transgenic mouse bioassay at oral doses up to 300 mg/kg/day.

Eszopiclone was clastogenic in in vitro (mouse lymphoma and chromosomal aberration) assays in mammalian cells. Eszopiclone was negative in the in vitro bacterial gene mutation (Ames) assay and in an in vivo micronucleus assay.

(S)-N-desmethyl zopiclone, a metabolite of eszopiclone, was positive in in vitro chromosomal aberration assays in mammalian cells. (S)-N-desmethyl zopiclone was negative in the in vitro bacterial gene mutation (Ames) assay and in an invivo chromosomal aberration and micronucleus assay.

Oral administration of eszopiclone to rats prior to and during mating, and continuing in females to day 7 of gestation (doses up to 45 mg/kg/day to males and females or up to 180 mg/kg/day to females only) resulted in decreased fertility, with no pregnancy at the highest dose tested when both males and females were treated. In females, there was an increase in abnormal estrus cycles at the highest dose tested. In males, decreases in sperm number and motility and increases in morphologically abnormal sperm were observed at the mid and high doses. The no-effect dose for adverse effects on fertility (5 mg/kg/day) is 16times the MRHD on a mg/m² basis.

## 6. Pharmaceutical Particulars

### 6.1. List of Excipients

Lactose monohydrate, Microcrystalline cellulose, Dibasic calcium phosphate dihydrate, Croscarmellose sodium, Hypromellose, Magnesium stearate, Opadry Blue 03G505001& Opadry White 03G58632.

**Composition of Opadry Blue 03G505001:**

| S.No. | Ingredients | Reference to quality standards | % w/w |
|---|---|---|---|
| 1. | Hypromellose | USP/ Ph. Eur/JP | 62.50 |
| 2. | Macrogol | NF/ Ph. Eur/JP | 8.00 |
| 4. | Titanium dioxide | USP/ Ph. Eur/JP/ FCC | 14.95 |
| 5. | Triacetin | USP/ Ph. Eur/ JPE/ FCC | 6.25 |
| 6. | FD & C Blue # Indigo carmine Aluminium Lake | -- | 8.30 |

**Composition of Opadry White 03G58632/Instacoat Universal White A05G13014**

| Sr. No. | Ingredients | % w/w | Function |
|---|---|---|---|
| 1 | HPMC 2910/Hypromellose 6cP (USP/ Ph.Eur./JP) | 62.50 | Film coating agent |
| 2 | Macrogol /PEG 3350 (NF/Ph.Eur./Macrogol 4000 JP) | 8.000 | Plasticizer |
| 3 | Titanium Dioxide (USP/FCC/ Ph.Eur./JP) | 23.250 | Opacifier |
| 4 | Triacetin (USP/Ph.Eur./FCC/JPE) | 6.250 | Plasticizer |

**6.2. Incompatibilities**
None

**6.3. Shelf life**
24 months from the manufacturing date.
Never use after the expiry date clearly indicated on the outer packaging.

**6.4. Special precautions for storage**
Store below 30°C in a dry place. Protect from light.

**6.5. Nature and contents of container**
HDPE Bottle of 100 Tablets, such 1 HDPE bottle is packed in a carton along withpackage insert.

Following minimum batch details is coded on foil and Carton Batch No., Mfg. Date and Exp. Date.

**6.6. Special Precaution for disposal**
None

**7. Supplier**
**Macleods Pharmaceuticals Limited**
304, Atlanta Arcade, Marol
Church Road, Andheri
(East), Mumbai- 400 059,
India.
Phone: +91-22-66762800
Fax: +91-22-2821 6599
E-mail: exports@macleodsphara.com

**8. Marketing Authorization Number**
TAN 22 HM 0041

**9.** Date of First <Registration> / Renewal of the <Registration>
10/01/2022

**10. Date of Revision of the Text**