SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product
Eszopiclone 3 mg film-coated tablets
Zopimac 3

2. Qualitative and quantitative composition
Each tablet contains 3 mg of eszopiclone.

Excipient with known effect
Each tablet also contains 55.80 mg of lactose monohydrate. See section 4.4.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form
Tablet.

Dark blue-coloured, round-shaped, biconvex, film-coated tablet debossed with 'L' on one side and plain on the other side.

4. Clinical particulars

4.1 Therapeutic indications
Eszopiclone is indicated for the treatment of insomnia.

4.2 Posology and method of administration
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 the 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.

Geriataric or debilitated Patients
In patients with severe hepatic impairment, or patients coadministered 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 to reduce the effect of eszopiclone on sleep latency.

4.3 Contraindications

Hypersensitivity to the active substance or any of the excipients listed in section 6.1.
Hypersensitivity reactions include anaphylaxis and angioedema [see section 4.4].

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 some patients at 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 mg eszopiclone 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 in the middle of the night is not recommended.

The risk of next-day psychomotor impairment is increased if eszopiclone is taken with 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 Diagnose

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 insomnia or the emergence of new thinking or behaviour 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 rechallenged with the drug.

Abnormal Thinking and Behavioral Changes
A variety of abnormal thinking and behaviour changes have been reported to occur in association with the use of sedatives/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 behavioural changes have included bizarre behaviour, 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 behaviours 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 behaviours such as sleep-driving may occur with eszopiclone alone at therapeutic doses, the use of alcohol and other CNS depressants with eszopiclone appears to increase the risk of such behaviours, as does the use of eszopiclone at doses exceeding the maximum recommended 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 behaviours (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 behaviours listed above is drug-induced, spontaneous in origin, or a result of an underlying psychiatric or physical disorder. Nonetheless, the emergence of any new behavioural 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.

A study in healthy volunteers did not reveal respiratory-depressant effects at doses 2.5-fold higher (7 mg) than the recommended dose of eszopiclone. 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 in the 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**.**

Excipients
This medicine 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 medicinal products and other forms of interaction

CNS Active Drugs
Ethanol: An additive effect on psychomotor performance was seen with the coadministration of eszopiclone and ethanol.
Olanzapine: Coadministration of eszopiclone and olanzapine produced a decrease in DSST scores. The interaction was pharmacodynamic; there was no alteration in the pharmacokinetics of either drug.

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

Drugs that Induce CYP3A4 (Rifampicin)
Racemic zopiclone exposure was decreased by 80% by concomitant use of rifampicin, a potent inducer of CYP3A4. A similar effect would be expected with eszopiclone. Combination use with

CYP3A4 inducer may decrease the exposure and effects of eszopiclone.

4.6 Fertility, pregnancy and lactation

Pregnancy
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. Oral administration of eszopiclone to pregnant rats (62.5, 125, or 250 mg/kg/day) and rabbits (4, 8, or 16 mg/kg/day) throughout organogenesis showed no evidence of teratogenicity up to the highest doses tested. In rats, reduced fetal weight and increased incidences of skeletal variations and/or delayed ossification were observed at the mid and high doses. The no-observed-effect dose for adverse effects on embryofetal development is 200 times the maximum recommended human dose (MRHD) of 3 mg/day on a mg/m2 basis. No effects on embryofetal development were observed in rabbits; the highest dose tested is approximately 100 times the MRHD on a mg/m2 basis.

Oral administration of eszopiclone (60, 120, or 180 mg/kg/day) to pregnant rats throughout the pregnancy and lactation resulted in increased post-implantation loss, decreased postnatal pup weights and survival, and increased pup startle response at all doses. The lowest dose tested is approximately 200 times the MRHD on a mg/m2 basis. Eszopiclone had no effects on other developmental measures or reproductive function in the offspring.

Breastfeeding
It is not known whether this drug is excreted in human milk.

4.7 Effects on the ability to drive and use machines

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 which may have a negative influence on the ability to drive and use machines.

4.8 Undesirable effects

Adverse reactions
The premarketing development program for eszopiclone included eszopiclone exposures in patients and/or normal subjects from two different groups of studies: approximately 400 normal subjects in clinical pharmacology/pharmacokinetic studies, and approximately 1550 patients in placebo-controlled clinical effectiveness studies, corresponding to approximately 263 patient- exposure years. The conditions and duration of treatment with eszopiclone varied greatly and included (in overlapping categories) open-label and double-blind phases of studies, inpatients and outpatients, and short-term and longer-term exposure. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, and ECGs.
The stated frequencies of adverse reactions represent the proportion of individuals who experienced, at least once, adverse reactions of the type listed. A reaction was considered treatment-emergent if it occurred for the first time or worsened while the patient was receiving therapy following baseline

evaluation.

Clinical Trials Experience

Adverse Reactions Resulting in Discontinuation of Treatment
In placebo-controlled, parallel-group clinical trials in the elderly, 3.8% of 208 patients who received placebo, 2.3% of 215 patients who received 2 mg eszopiclone, and 1.4% of 72 patients who received 1 mg eszopiclone discontinued treatment due to an adverse reaction. In the 6-week parallel-group study in adults, no patients in the 3 mg arm discontinued because of an adverse reaction. In the long-term 6-month study in adult insomnia patients, 7.2% of 195 patients who received a placebo and 12.8% of 593 patients who received 3 mg eszopiclone discontinued due to an adverse reaction. No reaction that resulted in discontinuation occurred at a rate of greater than 2%.

Adverse Reactions Observed at an Incidence of ≥2% in Controlled Trials
Table 1 shows the incidence of adverse reactions from a Phase 3 placebo-controlled study of eszopiclone at doses of 2 or 3 mg in non-elderly adults. The treatment duration in this trial was 44 days. The table includes only reactions that occurred in 2% or more of patients treated with eszopiclone 2 mg or 3 mg in which the incidence in patients treated with eszopiclone was greater than the incidence in placebo-treated patients.

Table 1: Incidence (%) of Adverse Reactions in a 6-week Placebo-Controlled Study in Non-Elderly Adults with Eszopiclone [1]

Adverse Reaction	**Placebo (n=99)**	**Eszopiclone 2 mg (n=104)**	**Eszopiclone 3 mg (n=105)**
Body as a Whole			
Headache	13	21	17
Viral Infection	1	3	3
Digestive System			
Dry Mouth	3	5	7
Dyspepsia	4	4	5
Nausea	4	5	4
Vomiting	1	3	0
Nervous System			
Anxiety	0	3	1
Confusion	0	0	3

Depression	0	4	1
Dizziness	4	5	7
Hallucinations	0	1	3
Libido Decreased	0	0	3
Nervousness	3	5	0
Somnolence	3	10	8
Respiratory System			
Infection	3	5	10
Skin and Appendages			
Rash	1	3	4
Special Senses			
Unpleasant Taste	3	17	34
Urogenital System			
Dysmenorrhea *	0	3	0
Gynecomastia **	0	3	0

1 Reactions for which the eszopiclone incidence was equal to or less than placebo are not listed on the table but included the following: abnormal dreams, accidental injury, back pain, diarrhoea, flu syndrome, myalgia, pain, pharyngitis, and rhinitis.
* Gender-specific adverse reactions in females
** Gender-specific adverse reaction in males

Adverse reactions from Table 1 that suggest a dose-response relationship in adults include viral infection, dry mouth, dizziness, hallucinations, infection, rash, and unpleasant taste, with this relationship clearest for unpleasant taste.

Table 2 shows the incidence of adverse reactions from combined Phase 3 placebo-controlled studies of eszopiclone at doses of 1 or 2 mg in elderly adults (ages 65-86). The treatment duration in these trials was 14 days. The table includes only reactions that occurred in 2% or more of patients treated with eszopiclone 1 mg or 2 mg in which the incidence in patients treated with eszopiclone was greater than the incidence in placebo-treated patients.

Table 2: Incidence (%) of Adverse Reactions in Elderly Adults (Ages 65-86) in 2-week Placebo-Controlled Trials with Eszopiclone [1]

Adverse Reactions	Placebo (n=208)	Eszopiclone 1 mg (n=72)	Eszopiclone 2 mg (n=215)
Body as a Whole			
Accidental Injury	1	0	3
Headache	14	15	13
Pain	2	4	5
Digestive System			
Diarrhea	2	4	2
Dry Mouth	2	3	7
Dyspepsia	2	6	2
Nervous System			
Abnormal Dreams	0	3	1
Dizziness	2	1	6
Nervousness	1	0	2
Neuralgia	0	3	0
Skin and Appendages			
Pruritus	1	4	1
Special Senses			
Unpleasant Taste	0	8	12
Urogenital System			
Urinary Tract Infection	0	3	0

1 Reactions for which the eszopiclone incidence was equal to or less than placebo are not listed on the table but included the following: abdominal pain, asthenia, nausea, rash, and somnolence.

Adverse reactions from Table 2 that suggest a dose-response relationship in elderly adults include pain, dry mouth, and unpleasant taste, with this relationship again clearest for unpleasant taste. These figures cannot be used to predict the incidence of adverse reactions in the course of usual medical practice because patient characteristics and other factors may differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contributions of drug and non-drug factors to the adverse reaction incidence rate in the population studied.

Other Reactions Observed During the Premarketing Evaluation of eszopiclone
Following is a list of modified COSTART terms that reflect adverse reactions as defined in the introduction to the *Adverse Reactions* section and reported by approximately 1550 subjects treated with eszopiclone at doses in the range of 1 to 3.5 mg/day during Phase 2 and 3 clinical trials throughout the United States and Canada. All reported reactions are included except those already listed in Tables 1 and 2 or elsewhere in labelling, minor reactions common in the general population, and reactions unlikely to be drug-related. Although the reactions reported occurred during treatment with eszopiclone, they were not necessarily caused by it.

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; **infrequent** adverse reactions are those that occurred in fewer than 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 oedema, 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, stomach ulcer, stomatitis, tongue oedema, rectal haemorrhage.

Hemic and Lymphatic System: **Infrequent:** anaemia, lymphadenopathy.

Metabolic and Nutritional: **Frequent:** peripheral oedema; **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, skin discolouration, sweating, urticaria; **Rare:** erythema multiforme, furunculosis, herpes zoster, hirsutism, maculopapular rash, vesiculobullous rash.

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

Urogenital System: **Infrequent:** 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 haemorrhage, vaginal haemorrhage, vaginitis; **Rare:** oliguria, pyelonephritis, urethritis.

Post-marketing
In addition to the adverse reactions observed during clinical trials, dysosmia, an olfactory dysfunction that is characterized by distortion of the sense of smell, has been reported during post-marketing surveillance with eszopiclone. Because this event is reported spontaneously from a population of unknown size, it is not possible to estimate the frequency of this event.

Special populations

Paediatric populations
The safety and effectiveness of eszopiclone have not been established in pediatric patients. Eszopiclone failed to demonstrate efficacy in controlled clinical studies of pediatric patients with Attention-Deficit/Hyperactivity (ADHD) associated insomnia.

In a 12-week controlled study, 483 pediatric patients (aged 6-17 years) with insomnia associated with ADHD (with 65% of the patients using concomitant ADHD treatments) were treated with oral tablets of eszopiclone (1 or 2 or 3 mg tablets, n=323), or placebo (n=160). Eszopiclone did not significantly decrease latency to persistent sleep, compared to placebo, as measured by polysomnography after 12 weeks of treatment. Psychiatric and nervous system disorders comprised the most frequent treatment-emergent adverse reactions observed with eszopiclone versus placebo and included dysgeusia (9% vs. 1%), dizziness (6% vs. 2%), hallucinations (2% vs. 0%) and suicidal ideation (0.3% vs. 0%). Nine patients on eszopiclone (3%) discontinued treatment due to an adverse reaction compared to 3 patients on placebo (2%).

In studies in which eszopiclone (2 to 300 mg/kg/day) was orally administered to young rats from weaning through sexual maturity, neurobehavioral impairment (altered auditory startle response) and reproductive toxicity (adverse effects on male reproductive organ weights and histopathology) were observed at doses ≥ 5 mg/kg/day. Delayed sexual maturation was noted in males and females at ≥ 10 mg/kg/day. The no-effect dose (2 mg/kg) was associated with plasma exposures (AUC) for eszopiclone and metabolite (S)-desmethylzopiclone [(S)-DMZ] approximately 2 times plasma exposures in humans at the maximum recommended dose (MRHD) in adults (3 mg/day).

When eszopiclone (doses from 1 to 50 mg/kg/day) was orally administered to young dogs from weaning through sexual maturity, neurotoxicity (convulsions) was observed at doses ≥ 5 mg/kg/day. Hepatotoxicity (elevated liver enzymes and hepatocellular vacuolation and degeneration) and reproductive toxicity (adverse effects on male reproductive organ weights and histopathology) were noted at a dose oϕ ≥10 mg/kg/day. The no-effect dose (1 mg/kg) was associated with plasma exposures (AUC) to eszopiclone and (S)-DMZ approximately 3 and 2 times, respectively, plasma exposures in humans at the MRHD in adults.

Geriatric use
A total of 287 subjects in double-blind, parallel-group, placebo-controlled clinical trials who received eszopiclone were 65 to 86 years of age. The overall pattern of adverse events for elderly subjects (median age = 71 years) in 2-week studies with nighttime dosing of 2 mg eszopiclone was not different from that seen in younger adults [see Adverse Reactions (6)]. Eszopiclone 2 mg exhibited a significant reduction in sleep latency and improvement in sleep maintenance in the elderly population. Compared with non-elderly adults, subjects 65 years and older had longer elimination and higher total exposure to eszopiclone. Therefore, dose reduction is recommended in elderly patients.

Hepatic impairment
No dose adjustment is necessary for patients with mild-to-moderate hepatic impairment. Exposure was increased in severely impaired patients compared with the healthy volunteers. The dose of eszopiclone should not exceed 2 mg in patients with severe hepatic impairment. Eszopiclone should be used with caution in patients with hepatic impairment.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the e-PV desktop applications (https://drive.google.com/file/d/16hwTz0587ZWtSWadbBAMwQPOD_KSExZP/view) or search for e-PV Mobile applications on the Google Play or Apple App Store.

4.9 Overdose
In clinical trials with eszopiclone, one case of overdose with up to 36 mg of eszopiclone was reported in which the subject fully recovered. Since commercial marketing began, spontaneous cases of eszopiclone overdoses up to 270 mg (90 times the maximum recommended dose of eszopiclone) have been reported, in which patients have recovered. Fatalities related to eszopiclone overdoses were reported only in combination with other CNS drugs or alcohol.

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 European 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. The physician may wish to consider contacting a poison control centre for up-to-date information on the management of hypnotic drug product overdosage.

5. Pharmacological properties

5.1 Pharmacodynamic properties
Pharmacological classification: 13.3 Hypnotics.

Mechanism of action
Eszopiclone is a nonbenzodiazepine hypnotic agent that is a pyrrolopyrazine derivative of the cyclopyrrolone class. The chemical name of eszopiclone is (+)-(5S)-6-(5- chloropyridin-2-yl)-7-oxo-6,7-dihydro-5H-pyrrolo[3,4-b] pyrazin-5-yl 4-methylpiperazine-1- carboxylate. 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 nonbenzodiazepine hypnotic that is a pyrrolopyrazine derivative of the cyclopyrrolone class with a chemical structure unrelated to pyrazolopyrimidines, imidazopyridines, benzodiazepines, barbiturates, or other drugs with known hypnotic properties.

Pharmacokinetics
The pharmacokinetics of eszopiclone have been investigated in healthy subjects (adult and elderly) and patients with hepatic disease or renal disease. In healthy subjects, the pharmacokinetic profile was examined after single doses of up to 7.5 mg and after once-daily administration of 1, 3, and 6 mg for 7 days. Eszopiclone is rapidly absorbed, with a time-to-peak concentration (t_{max}) of approximately 1 hour and a terminal-phase elimination half-life ($t_{1/2}$) of approximately 6 hours. In healthy adults, eszopiclone does not accumulate with once-daily administration, and its exposure is dose-proportional over the range of 1 to 6 mg.

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 by oxidation 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 $t_{1/2}$ 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 a 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 C_{max} of 21%, and delayed T_{max} 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 after a high-fat/heavy meal.

Specific Populations
Age
Compared with non-elderly adults, subjects 65 years and older had an increase of 41% in total exposure (AUC) and a slightly prolonged elimination of eszopiclone ($t_{1/2}$ approximately 9 hours). C_{max} was unchanged. Therefore, in elderly patients, the dose should not exceed 2 mg.

Gender
The pharmacokinetics of eszopiclone in men and women are similar.

Race
In an analysis of data on all subjects participating in Phase 1 studies of eszopiclone, the pharmacokinetics for all races studied appeared similar.

Hepatic Impairment
Pharmacokinetics of a 2 mg eszopiclone dose were assessed in 16 healthy volunteers and 8 subjects with mild, moderate, and severe liver disease. Exposure was increased 2-fold in severely impaired patients compared with the healthy volunteers. C_{max} and t_{max} were unchanged. No dose adjustment is necessary for patients with mild-to-moderate hepatic impairment. Dose reduction is recommended for patients with severe hepatic impairment. Eszopiclone should be used with caution in patients with hepatic impairment.

Renal Impairment
The pharmacokinetics of eszopiclone were studied in 24 patients with mild, moderate, or severe renal impairment. AUC and C_{max} were similar in the patients compared with demographically matched healthy control subjects. No dose adjustment is necessary in patients with renal impairment,

since less than 10% of the orally administered eszopiclone dose is excreted in the urine as the parent drug.

Drug Interactions
Eszopiclone is metabolized by CYP3A4 and CYP2E1 via demethylation and oxidation. There were no pharmacokinetic or pharmacodynamic interactions between eszopiclone and paroxetine. When eszopiclone was coadministered with olanzapine, no pharmacokinetic interaction was detected in levels of eszopiclone or olanzapine, but a pharmacodynamic interaction was seen on a measure of psychomotor function. Eszopiclone and lorazepam decreased each other's C_{max} by 22%. Coadministration of eszopiclone 3 mg to subjects receiving ketoconazole, a potent inhibitor of CYP3A4, 400 mg daily for 5 days, resulted in a 2.2-fold increase in exposure to eszopiclone. C_{max} and $t_{1/2}$ were increased 1.4-fold and 1.3-fold, respectively. Eszopiclone would not be expected to alter the clearance of drugs metabolized by common CYP450 enzymes.

Paroxetine: Coadministration of a single dose of eszopiclone and paroxetine produced no pharmacokinetic or pharmacodynamic interaction. The lack of a drug interaction following single-dose administration does not predict the complete absence of a pharmacodynamic effect following chronic administration.

Lorazepam: Coadministration of single doses of eszopiclone and lorazepam did not have clinically relevant effects on the pharmacodynamics or pharmacokinetics of either drug. The lack of a drug interaction following single-dose administration does not predict the complete absence of a pharmacodynamic effect following chronic administration.

Drugs with a Narrow Therapeutic Index
Digoxin: A single dose of eszopiclone 3 mg did not affect the pharmacokinetics of digoxin measured at steady state following dosing of 0.5 mg twice daily for one day and 0.25 mg daily for the next 6 days.
Warfarin: Eszopiclone 3 mg administered daily for 5 days did not affect the pharmacokinetics of (*R*)- or (*S*)-warfarin, nor were there any changes in the pharmacodynamic profile (prothrombin time) following a single 25 mg oral dose of warfarin.

Drugs Highly Bound to Plasma Protein
Eszopiclone is not highly bound to plasma proteins (52-59% bound); therefore, the disposition of eszopiclone is not expected to be sensitive to alterations in protein binding. Administration of eszopiclone 3 mg to a patient taking another highly protein-bound drug would not be expected to cause an alteration in the free concentration of either drug.

Clinical studies
The effect of eszopiclone on reducing sleep latency and improving sleep maintenance was established in studies with 2100 subjects (ages 18-86) with chronic and transient insomnia in six placebo-controlled trials of up to 6 months duration. Two of these trials were in elderly patients (n=523). Overall, at the recommended adult dose (2-3 mg) and elderly dose (1-2 mg), eszopiclone significantly decreased sleep latency and improved measures of sleep maintenance (objectively measured as wake time after sleep onset [WASO] and subjectively measured as total sleep time).

Transient insomnia
Healthy adults were evaluated in a model of transient insomnia (n=436) in a sleep laboratory in a double-blind, parallel-group, single-night trial comparing two doses of eszopiclone and a placebo. Eszopiclone 3 mg was superior to placebo on measures of sleep latency and sleep maintenance, including polysomnographic (PSG) parameters of latency to persistent sleep (LPS) and WASO.

Chronic insomnia
The effectiveness of eszopiclone was established in five controlled studies of chronic insomnia. Three controlled studies were in adult subjects, and two controlled studies were in elderly subjects with chronic insomnia.

Adults
In the first study, adults with chronic insomnia (n=308) were evaluated in a double-blind, parallel-group trial of 6 weeks duration comparing eszopiclone 2 mg and 3 mg with placebo. Objective endpoints were measured for 4 weeks. Both 2 mg and 3 mg were superior to placebo on LPS at 4 weeks. The 3 mg dose was superior to placebo on WASO.

In the second study, adults with chronic insomnia (n=788) were evaluated using subjective measures in a double-blind, parallel-group trial comparing the safety and efficacy of eszopiclone 3 mg with a placebo administered nightly for 6 months. Eszopiclone was superior to placebo on subjective measures of sleep latency, total sleep time, and WASO.

In addition, a 6-period cross-over PSG study evaluating eszopiclone doses of 1 to 3 mg, each given over 2 days, demonstrated the effectiveness of all doses on LPS, and of 3 mg on WASO. In this trial, the response was dose-related.

Elderly
Elderly subjects (ages 65-86) with chronic insomnia were evaluated in two double-blind, parallel-group trials of 2 weeks duration. One study (n=231) compared the effects of eszopiclone with placebo on subjective outcome measures and the other (n=292) on objective and subjective outcome measures. The first study compared 1 mg and 2 mg of eszopiclone with placebo, while the second study compared 2 mg of eszopiclone with placebo. All doses were superior to placebo on measures of sleep latency. In both studies, 2 mg of eszopiclone was superior to placebo on measures of sleep maintenance.

Studies pertinent to safety concerns for sedative-hypnotic drugs

Next-Day Residual Effects
In a double-blind study of 91 healthy adults aged 25- to 40 years, the effects of eszopiclone 3 mg on psychomotor function were assessed between 7.5 and 11.5 hours the morning after dosing. Measures included tests of psychomotor coordination that are correlated with the ability to maintain a motor vehicle in the driving lane, tests of working memory, and subjective perception of sedation and coordination. Compared with a placebo, eszopiclone 3 mg was associated with next-morning psychomotor and memory impairment that was most severe at 7.5 hours, but still present and potentially clinically meaningful at 11.5 hours. Subjective perception of sedation and coordination

from eszopiclone 3 mg was not consistently different from placebo, even though subjects were objectively impaired.

In a 6-month double-blind, placebo-controlled trial of nightly administered eszopiclone 3 mg, memory impairment was reported by 1.3% (8/593) of subjects treated with eszopiclone 3 mg compared to 0% (0/195) of subjects treated with placebo. In a 6-week adult study of nightly administered eszopiclone confusion was reported by 3.0% of patients treated with eszopiclone 3 mg, compared to 0% of subjects treated with placebo. In the same study, memory impairment was reported by 1% of patients treated with either 2 mg or 3 mg eszopiclone, compared to 0% treated with placebo.

In a 2-week study of 264 elderly insomniacs, 1.5% of patients treated with eszopiclone 2 mg reported memory impairment compared to 0% treated with placebo. In another 2-week study of 231 elderly insomniacs, 2.5% of patients treated with eszopiclone 2 mg reported confusion compared to 0% treated with placebo.

Withdrawal-Emergent Anxiety and Insomnia

During nightly use for an extended period, pharmacodynamic tolerance or adaptation has been observed with other hypnotics. If a drug has a short elimination half-life, a relative deficiency of the drug or its active metabolites (i.e., in relationship to the receptor site) may occur at some point in the interval between each night's use. This is believed to be responsible for two clinical findings reported to occur after several weeks of nightly use of other rapidly eliminated hypnotics: increased wakefulness during the last quarter of the night and the appearance of increased signs of daytime anxiety.

In a 6-month double-blind, placebo-controlled study of nightly administration of eszopiclone 3 mg, rates of anxiety reported as an adverse event were 2.1% in the placebo arm and 3.7% in the eszopiclone arm. In a 6-week adult study of nightly administration, anxiety was reported as an adverse event in 0%, 2.9%, and 1.0% of the placebo, 2 mg, and 3 mg treatment arms, respectively. In this study, a single-blind placebo was administered on nights 45 and 46, the first and second days of withdrawal from the study drug. New adverse events were recorded during the withdrawal period, beginning with day 45, and up to 14 days after discontinuation. During this withdrawal period, 105 subjects previously taking nightly eszopiclone 3 mg for 44 nights spontaneously reported anxiety (1%), abnormal dreams (1.9%), hyperesthesia (1%), and neurosis (1%), while none of 99 subjects previously taking placebo reported any of these adverse events during the withdrawal period. Rebound insomnia, defined as a dose-dependent temporary worsening in sleep parameters (latency, sleep efficiency, and number of awakenings) compared with baseline following discontinuation of treatment, is observed with short- and intermediate-acting hypnotics.

Rebound insomnia following discontinuation of eszopiclone relative to placebo and baseline was examined objectively in a 6-week adult study on the first 2 nights of discontinuation (nights 45 and 46) following 44 nights of active treatment with 2 mg or 3 mg. In the eszopiclone 2 mg group, compared with baseline, there was a significant increase in WASO and a decrease in sleep efficiency, both occurring only on the first night after discontinuation of treatment. No changes from baseline were noted in the eszopiclone 3 mg group on the first night after discontinuation, and there was a significant improvement in LPS and sleep efficiency compared with baseline following the

second night of discontinuation. Comparisons of changes from baseline between eszopiclone and placebo were also performed. On the first night after discontinuation of eszopiclone 2 mg, LPS and WASO were significantly increased and sleep efficiency was reduced; there were no significant differences on the second night. On the first night following discontinuation of eszopiclone 3 mg, sleep efficiency was significantly reduced. No other differences from placebo were noted in any other sleep parameter on either the first or second night following discontinuation. For both doses, the discontinuation-emergent effect was mild, had the characteristics of the return of the symptoms of chronic insomnia, and appeared to resolve by the second night after eszopiclone discontinuation.

5.3 Preclinical safety data

Carcinogenesis
In a carcinogenicity study in rats, oral administration of eszopiclone for 97 (males) or 104 (females) weeks resulted in no increases in tumours; 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 tumours 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 tumours were due to skin lesions induced by aggressive behaviour, 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 an overall assessment of carcinogenic potential, no increases in either pulmonary or skin tumours were seen at doses producing plasma levels of eszopiclone approximately 90 times those in humans at the MRHD of eszopiclone (and 12 times the exposure in the racemate study). Eszopiclone did not increase tumours in a p53 transgenic mouse bioassay at oral doses up to 300 mg/kg/day.

Mutagenesis
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 *in vivo* chromosomal aberration and micronucleus assay.

Impairment of Fertility
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 16 times the MRHD on a mg/m^2 basis.

6. Pharmaceutical particulars

6.1 List of excipients
Lactose monohydrate
Hypromellose
Microcrystalline cellulose
Croscarmellose sodium
Dibasic calcium phosphate dihydrate
Colloidal silicon dioxide
Magnesium stearate
Opadry blue 03G505001
Purified water

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
24 months.

6.4 Special precautions for storage
Store below 30°C.

6.5 Nature and contents of the container
The tablets are packed in a white, round, HDPE bottle closed with a white child-resistant closure with a pulp and heat seal liner.

Pack size: 100’s.

6.6 Special precautions for disposal and handling
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. APPLICANT
Macleods Pharmaceuticals Ltd.
304, Atlanta Arcade,
Marol Church Road,
Andheri (East), Mumbai - 400059

India

8. MANUFACTURERS

Macleods Pharmaceuticals Limited.
Block No.: N-2, Village Theda, P.O. Lodhi Majra, Tehsil Baddi,
Dist.: Solan, Himachal Pradesh
India

9. REGISTRATION DETAILS

Zimbabwe registration number: 2023/13.3/6486
Zimbabwe category for distribution: Prescription Preparations (P.P.)

10. DATE OF REVISION OF TEXT

November 2023