SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Lunivia 3 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 3 mg eszopiclone.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

Blue, round, biconvex film-coated tablets, debossed with “3” marking on one side and an average diameter of about 6.5 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Lunivia is indicated for the treatment of insomnia, in adults, usually for short-term duration.

Benzodiazepines or benzodiazepine-like substances are only indicated when the disorder is severe, disabling or subjecting the individual to extreme distress.

4.2 Posology and method of administration

Prior to starting treatment with eszopiclone a discussion should be held with patients to put in place a strategy for ending treatment with this medicine in order to minimise the risk of dependence, addiction and drug withdrawal syndrome (see section 4.4).

Treatment should be given for the shortest possible duration.

Eszopiclone should be taken in a single intake immediately at bedtime and not be re-administered during the same night.

Posology

Adults: The recommended starting dose is 1 mg. The dose can be increased to 2 mg or 3 mg if clinically indicated. The lowest effective dose should be used. The total dose of eszopiclone should not exceed 3 mg.

The length of treatment should be for the minimum duration necessary for effective treatment. Typically, this will be no more than four weeks including the period of tapering off. In certain cases, for example in patients with chronic insomnia, it may be necessary to extend the treatment period up to a maximum duration of 6 months (see section 5.1). This requires regular monitoring and evaluation of the patient's condition since the risk of abuse and dependence increases with the duration of treatment (see section 4.4).

Use with potent CYP3A4 inhibitors
In elderly patients (> 65 years of age) receiving concomitant potent CYP3A4 inhibitors, eszopiclone is contraindicated (see section 4.3). In other adult patients, the dose must not exceed 2 mg.

Use with CNS depressants
A dose reduction for eszopiclone may be necessary when it is co-administered with other CNS depressants because of the potentially additive effects (see section 4.5).

Elderly aged 65 or older:
The recommended starting dose for elderly patients is 1 mg immediately before bedtime. In these patients, the dose may be increased to 2 mg if clinically indicated.

The recommended dose must not be exceeded (see section 5.2).

Hepatic impairment:
No dose adjustment is required in patients with mild to moderate hepatic impairment (see section 5.2). In patients with severe hepatic insufficiency, eszopiclone is contraindicated as it may precipitate encephalopathy (see section 4.3 and section 5.2).

Renal impairment:
No dose adjustment is required in patients with mild to moderate renal impairment (see section 5.2).

The maximum recommended dose of eszopiclone in patients with severe renal impairment is 2 mg.

Paediatric population:
Eszopiclone should not be used in children and adolescents less than 18 years (see section 4.3).
The safety and efficacy of eszopiclone in children and adolescents have not been established.

Method of administration
Lunivia is for oral use.
The tablets must not be crushed or broken prior to ingestion.

4.3 Contraindications

- Hypersensitivity to the active substance, to zopiclone or to any of the excipients listed in section 6.1.
- Myasthenia gravis

- Severe respiratory insufficiency
- Severe sleep apnoea syndrome
- Severe hepatic insufficiency
- Patient who have experienced complex sleep behaviours after taking eszopiclone, zopiclone or

  any other hypnotic agents (see section 4.4).
- Elderly patients receiving concomitant potent CYP3A4 inhibitors (see section 4.5)
- Children and adolescent under 18 years of age.

4.4 Special warnings and precautions for use

General
The cause of insomnia should be identified wherever possible. The underlying factors should be treated before a hypnotic is prescribed. The lack of relief from insomnia after a 7-14 day course of treatment may indicate the presence of a primary psychiatric or physical disorder and the patient should be carefully re-evaluated.

Chronic respiratory impairment
Caution should be observed when prescribing eszopiclone to patients with respiratory insufficiency since benzodiazepines and benzodiazepine-like substances have been shown to impair respiratory drive. A lower dose is recommended for patients with chronic respiratory insufficiency due to the risk of respiratory depression.

Risk from concomitant use of opioids
Concomitant use of eszopiclone and opioids may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing of sedative medicines such as benzodiazepines or related medicinal products such as eszopiclone with opioids should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe eszopiclone concomitantly with opioids, the lowest effective dose should be used, and the duration of treatment should be as short as possible (see also general dose recommendation in section 4.2).

The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers (where applicable) to be aware of these symptoms (see section 4.5).

Drug dependence, tolerance and potential for abuse

Drug addiction comprises behavioural, cognitive and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use and possible tolerance or physical dependence. Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, which manifests as withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug. Addiction and dependence are related but distinct presentations and in discussing these themes, terminology that apportion blame to the individual should be avoided.

For all patients, prolonged use of this product may lead to drug dependence and addiction but can occur with short-term use at recommended therapeutic doses. The risks are increased in individuals with current or past history of substance misuse disorder (including alcohol misuse) or mental health disorder (e.g., major depression).

Additional support and monitoring may be necessary when prescribing for patients at risk of drug misuse.

A comprehensive patient history should be taken to document concomitant medications, including over-the-counter medicines and medicines obtained on-line, and past and present medical and psychiatric conditions.

Patients may find that treatment is less effective with chronic use and express a need to increase the dose to obtain the same level of symptom control as initially experienced. Patients may also supplement their treatment with additional medications to achieve the same effect. These could be signs that the patient is developing tolerance. The risks of developing tolerance should be explained to the patient.

Overuse or misuse may result in overdose and/or death. It is important that patients only use medicines that are prescribed for them at the dose they have been prescribed and do not give this medicine to anyone else.

Patients should be closely monitored for signs of misuse, abuse, or addiction.
The clinical need for treatment with Lunivia should be reviewed regularly, with frequent assessments of patients being undertaken during the course of their treatment.

Drug withdrawal syndrome

Prior to starting treatment with Lunivia, a discussion should be held with patients to explain the risk of dependence, addiction, and drug withdrawal syndrome. A withdrawal strategy for ending treatment with Lunivia should also be put in place with the patient before starting treatment (there may be exceptions to this in specific clinical situations such as symptom management in end of life palliative care).

Drug withdrawal syndrome may occur upon abrupt cessation of therapy or dose reduction. When a patient no longer requires therapy, it is advisable to taper the dose gradually to minimise symptoms of withdrawal. Tapering from a high dose may take in excess of weeks or months. Patients should be informed of this when the medication is first prescribed.

The reduction schedule for a patient should be tailored to the individual and should be modified to allow intolerable withdrawal symptoms to improve before making the next reduction. If using a published withdrawal schedule, apply it flexibly to accommodate the person’s preferences, changes to their circumstances and the response to dose reductions.

Suggest a slow stepwise rate of reduction proportionate to the existing dose, so that decrements become smaller as the dose is lowered, unless clinical risk is such that rapid withdrawal is needed.

If a patient develops withdrawal reactions, consider pausing the taper or increasing the dosage to the previous tapered dosage level.

For more information regarding potential withdrawal reactions, please see section 4.8 *Withdrawal syndrome*.

If women take this drug during pregnancy, there is a risk that their newborn infants will experience neonatal withdrawal syndrome.

Rebound insomnia
Rebound insomnia manifested as an increase in sleep latency for one to two nights has been observed following cessation of eszopiclone treatment. These events resolved without intervention. It is important that patients are aware of the possibility of rebound phenomena to minimise anxiety. To reduce the risk of rebound phenomena, the dose of eszopiclone should be decreased gradually.

Tolerance
In clinical studies with eszopiclone, no development of tolerance to any parameter of sleep measurements was observed during treatment periods of up to six months (see section 5.1).

Memory and psychomotor impairment
Benzodiazepines and benzodiazepine-like substances, such as eszopiclone, may induce anterograde amnesia and psychomotor impairment, including accidental injury and falls. In particular elderly patients may be more vulnerable to falls resulting in injuries such as hip fractures.

Amnesia usually occurs several hours after ingesting the medicinal product. In order to reduce the risk, patients should ensure that they will be able to have an uninterrupted sleep of at least 8 hours (see section 4.8).

The risk of next-day psychomotor impairment, including impaired driving ability, is increased if:

- eszopiclone is taken less than 12 hours before performing activities that require mental alertness (see section 4.7)
- a dose higher than the recommended dose is taken;
- eszopiclone is co-administered with other CNS depressants or with other drugs that increase the blood levels of eszopiclone, or with alcohol or illicit drugs (see section 4.5).

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 eszopiclone and in particular during the 12 hours following administration.

Depression and suicidality
Eszopiclone should be administered with caution in patients exhibiting symptoms of depression.
Eszopiclone is not a treatment for depression and may even unmask symptoms.
Benzodiazepines and benzodiazepine-like substances such as eszopiclone should not be used without appropriate treatment of the depression or anxiety associated with depression (suicide may be precipitated in such patients).
Since these disorders may be associated with suicidal tendencies, the smallest amount of eszopiclone should be supplied to these patients because of the possibility of intentional overdose (see section 5.1).

Several epidemiological studies showed an increased incidence of suicide and suicide attempt in patients with or without depression, who were treated with benzodiazepines or other hypnotics, including zopiclone. A causal relationship was not established.

Alcohol, substance and drug abuse/dependence
Eszopiclone should be used with extreme caution in patients with current or a history of alcohol, substance and/or drug abuse or dependence.

Psychiatric and "paradoxical" reactions

Reactions like restlessness, aggravated insomnia, agitation, irritability, aggressiveness, delusion, rages, nightmares, parasomnia, depersonalization, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects are known to occur when using benzodiazepines or benzodiazepine-like substances. They may be drug-induced, spontaneous in origin, or a result of an underlying psychiatric or physical disorder. These reactions are more likely to occur in the elderly. Any new behavioural sign or symptom requires careful and immediate evaluation and the use of eszopiclone should be discontinued.

Somnambulism and associated behaviours
Sleep walking and other associated behaviours such as "sleep driving", preparing and eating food, or making phone calls or having sex, with amnesia for the event, have been reported in patients who have taken eszopiclone and were not fully awake.
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. Discontinuation of eszopiclone should be strongly considered for patients who report such behaviours, due to the risk to the patient and others (see section 4.5 and section 4.8).

Lunivia contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use with alcohol should be avoided because the sedative effect of eszopiclone may be enhanced (see section 4.7).

In combination with other central nervous system (CNS) depressants (e.g., antipsychotics, anxiolytics, muscle-relaxants, antiepileptics and sedative antihistamines) an enhancement of the central sedation may occur. A dose reduction for eszopiclone may be necessary when it is co-administered with agents with known CNS-depressant effects such as olanzapine.

CYP3A4 is a major metabolic pathway for elimination of eszopiclone, with a secondary contribution from CYP2E1. Co-administration of potent inhibitors of CYP3A4 (such as other azole antimycotics, macrolide antibiotics, grapefruit juice) increase the plasma level of eszopiclone and thus may increase the hypnotic effect of eszopiclone (see section 4.4 and section 5.2). Furthermore, the exposure of eszopiclone was increased by approximately 2-fold by co-administration of ketoconazole 400 mg daily for 5 days, a potent inhibitor of CYP3A4. A dose reduction for eszopiclone may be required when it is co-administered with CYP3A4 inhibitors (see section 4.2). In elderly patients receiving concomitant potent CYP3A4 inhibitors, eszopiclone is contraindicated (see section 4.3).

Racemic zopiclone exposure was decreased 80% by concomitant use of rifampicin, a potent inducer of CYP3A4. A similar effect would be expected with eszopiclone and concomitant use with other strong inducers of cytochrome P450-enzymes such as carbamazepine, phenytoin and St John's Wort. A dose increase for eszopiclone may be required when it is co-administered with CYP3A4 inducers.

Eszopiclone did not affect the pharmacokinetic or pharmacodynamic profiles of paroxetine, digoxin, warfarin, or the pharmacodynamic profile of lorazepam.

In patients with mood disorders, co-administration of eszopiclone with fluoxetine or escitalopram did not adversely affect the pharmacodynamic effects of eszopiclone or the antidepressant medicinal product (see section 5.1).

Concomitant administration of benzodiazepine or benzodiazepine-like substances with narcotic analgesics may enhance their euphoric effect and could lead to an increase in physical dependence.

Opioids

The concomitant use of sedative medicines such as benzodiazepines or related drugs such as eszopiclone with opioids increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dosage and duration of concomitant use should be limited (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of eszopiclone in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Eszopiclone is not recommended during pregnancy and in women of childbearing potential not using contraception.

When racemic zopiclone is taken during the later stages of pregnancy, withdrawal symptoms may occur postnatally in the newborn. During the last trimester, there is a risk of adverse pharmacological effects on the foetus and/or the neonate, such as hypotonia, respiratory depression and hypothermia.

Breastfeeding

Animal and human studies have demonstrated transfer of racemic zopiclone into breast milk. It is not known whether eszopiclone or the metabolite (S)-N-desmethyl zopiclone are excreted in human milk. A risk to the suckling child cannot be excluded.

Eszopiclone should not be used during breast feeding.

Fertility

In human clinical studies no evidence of impaired fertility was observed in males and females after treatment for up to 6 months.

However, animal studies with eszopiclone showed impairment of male and female fertility in different species (see section 5.3). The influence of eszopiclone on human fertility after chronic administration (> 6 month) is unknown.

4.7 Effects on ability to drive and use machines

Because of its pharmacological properties and its effect on central nervous system, eszopiclone may adversely affect the ability to drive or to use machines. Sedation, amnesia, blurred vision, impaired concentration and impaired muscular function may adversely affect the ability to drive or to use machines. If insufficient sleep duration occurs, the likelihood of impaired alertness may be increased.

The risk of psychomotor impairment, including impaired driving ability, is increase if:

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

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 eszopiclone and in particular during the 12 hours following that administration. Driving ability impairment and behaviours such as 'sleep-driving' have occurred with eszopiclone alone at therapeutic doses (see section 4.4). Co-administration of eszopiclone with alcohol and other CNS depressants increases the risk of such behaviours (see section 4.4 and 4.5). Patients should be warned not to use alcohol or other psychoactive substances when taking eszopiclone.

4.8 Undesirable effects

Information presented on adverse reactions is based on experience from clinical trials of up to 6 months duration conducted with 1 to 3 mg eszopiclone or placebo in non-elderly adults. In these clinical trials a total of 1626 subjects were taking eszopiclone and 858 subjects were taking placebo. The most commonly reported adverse reaction was dysgeusia (unpleasant taste). Headache, somnolence, dry mouth, dizziness and nausea were also commonly observed (<10% of patients).

In the table below, adverse reactions which occurred at an incidence greater than placebo and in at least 2 patients are listed by system organ class and frequency: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100) and rare (≥1/10,000 to <1/1,000) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Infections and infestations
Uncommon: Infection, viral infection

Blood and lymphatic system disorders
Uncommon: Hypochromic anaemia, anaemia, leukopenia, eosinophilia

Immune system disorders
Uncommon: Allergic reaction

Rare:	Angiooedema*, anaphylactic reaction*

Endocrine disorders

Uncommon:	Hyperthyroidism

Metabolism and nutrition disorders

Uncommon:	Peripheral oedema, anorexia, thirst, increased appetite, hypokalaemia

Psychiatric disorders

Common:	Nervousness, depression, anxiety
Uncommon:	Emotional lability, libido decreased, confusion, agitation, hallucinations, insomnia, apathy, euphoria
Rare:	Irritability*, aggression*, restlessness*, delusion*, anger*, abnormal behaviour (possibly associated with amnesia)* and somnambulism (see section 4.4)
Not known:	Drug dependence (see section 4.4), withdrawal syndrome*, damped emotions*

Nervous system disorders

Very common:	Dysgeusia (unpleasant taste)
Common:	Headache, somnolence, dizziness, abnormal dreams, memory impairment, thinking abnormal
Uncommon:	Vertigo, ataxia, abnormal gait, incoordination, hypokinesia, paraesthesia, stupor, tremor
Not known:	Dysosmia, disturbance in attention*, prolonged reaction time*

Eye disorders

Common	Blurred vision (predominantly in elderly patients)
Uncommon:	Dry eyes
Not known:	Diplopia*

Ear and labyrinth disorders

Uncommon:	Tinnitus, ear pain

Vascular disorders

Common:	Migraine
Uncommon:	Hypertension, syncope

Respiratory, thoracic and mediastinal disorders

Common:	Pharyngitis
Uncommon:	Dyspnoea, rhinitis, hiccup
Not known:	Respiratory depression (see section 4.4)*

Gastrointestinal disorders

Common:	Dry mouth, diarrhoea, nausea, dyspepsia, abdominal pain, vomiting
Uncommon:	Halitosis, mouth ulceration, colitis, gastroenteritis, tongue oedema

Hepatobiliary disorders

Very rare:	Mild to moderate increased transaminases and/or blood alkaline phosphatase*

Skin and subcutaneous tissue disorders

Common:	Rash
Uncommon:	Photosensitivity reaction, sweating, acne, dry skin, eczema
Rare:	Pruritus (common in elderly patients)

Musculoskeletal and connective tissue disorders

Common:	Back pain, myalgia
Uncommon:	Leg cramps, muscle twitching, myasthenia, joint disorder
Not known:	Muscular weakness*

Renal and urinary disorders

Uncommon:	Urinary frequency increased, urinary tract infection, kidney pain, urinary incontinence, kidney calculus, albuminuria

Reproductive system and breast disorders

Uncommon:	Dysmenorrhea, metrorrhagia, breast pain, hypomenorrhea, impotence

General disorders and administration site conditions

Common:	Asthenia, pain
Uncommon:	Fever, fatigue*

Investigations

Uncommon:	Weight gain, weight loss

Injury, poisoning and procedural complications

Rare:	Fall (predominantly in elderly patients)*

*Adverse reactions that have not been reported for eszopiclone but with racemic zopiclone.

Amnesia
Anterograde amnesia may occur on recommended therapeutic doses, the risk is increased at higher doses. Amnestic effects may be combined with inappropriate behaviour (see section 4.4).

Depression
Pre-existing depression may be unmasked with the use of benzodiazepine or benzodiazepine-like agents.

Psychiatric and "paradoxical" reactions
Reactions like restlessness, agitation, irritability, decreased inhibition, aggressiveness, abnormal thinking, delusions, rages, nightmares, depersonalisation, hallucinations, psychoses, inappropriate behaviour, extroversion that seems out of character and other adverse behavioural reactions are known to occur when using benzodiazepines or benzodiazepine-like substances. Such reactions are more likely to occur in the elderly.

Dependence
Use (even at therapeutic doses) of benzodiazepines and benzodiazepine-like substances may lead to the development of physical dependence: discontinuation of therapy may result in withdrawal or rebound phenomena (see section 4.4). Psychological dependence may occur. Abuse of benzodiazepines and benzodiazepine-like substances has been reported.

Withdrawal syndrome
Withdrawal syndrome has been reported upon discontinuation of eszopiclone (see section 4.4). Withdrawal symptoms vary and may include rebound insomnia, muscle pain, anxiety, tremor, sweating, agitation, confusion, headache, palpitations, tachycardia, delirium, nightmares, hallucinations, panic attacks, muscle aches/cramps, increased appetite, gastrointestinal disturbances 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. In very rare cases, seizures may occur.

Elderly population
The adverse reaction profile in clinical trials with elderly patients with insomnia is generally similar to the profile observed in clinical trials with non-elderly patients with insomnia. Additional adverse reactions reported in the elderly were vision blurred (common) and pruritus (common).

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:

Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose
Patients should be informed of the signs and symptoms of overdose and to ensure that family and friends are also aware of these signs and to seek immediate medical help if they occur.

Overdose is usually manifested by varying degrees of central nervous system depression ranging from drowsiness to coma depending on the quantity ingested.
Symptomatic and supportive treatment is indicated in a suitable clinical environment. Particular attention should be paid to cardiovascular and respiratory functions. Gastric lavage is useful only when performed soon after ingestion. Although not evaluated, haemodialysis is not expected to be of value due to the large volume of distribution of eszopiclone. Flumazenil may be a useful antidote.

In clinical studies 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 overdose up to 270 mg have been reported.
Fatal overdose is more likely to occur when eszopiclone is taken in combination with other CNS depressants including alcohol. Subjects have recovered from overdose with up to 270 mg of eszopiclone alone.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Nervous system; psycholeptics; hypnotics and sedatives; Benzodiazepine related drugs,

ATC code: N05CF04

Mechanism of action

Eszopiclone is a non-benzodiazepine hypnotic agent, which is a pyrrolopyrazine derivative of the cyclopyrrolone class with a chemical structure unrelated to pyrazolopyrimidines, imidazopyridines, benzodiazepines or barbiturates. The precise mechanism of action of eszopiclone is unknown but its effect is believed to result

from modulation of gamma-aminobutyric acid (GABA)-A-receptor macromolecular complexes, containing alpha-1, alpha-2, alpha-3 and alpha-5 sub-units. It is believed to increase GABA evoked chloride conductance resulting in neuronal hyperpolarisation thereby inhibiting neuronal transmission and causing sleep.

Transient insomnia

In a single night model of transient insomnia in healthy adult volunteers, a 3 mg dose of eszopiclone was superior to placebo on measures of sleep onset and sleep maintenance using objective polysomnography. In addition, self-reported scores for sleep quality and sleep depth were significantly better for eszopiclone compared to placebo.

Primary insomnia

In placebo-controlled studies up to 6-months duration in subjects with chronic insomnia, eszopiclone demonstrated sustained improvement in sleep onset and nocturnal awakening measures, improved total sleep time, and sleep quality (restorative sleep) throughout the treatment duration as measured by objective polysomnography and subjective outcome measures. Next day function was improved by the administration of eszopiclone as assessed by a number of measures. No development of tolerance was observed in placebo-controlled studies in subjects with chronic insomnia treated with eszopiclone for up to 6 months duration and in subjects with insomnia or co-morbid conditions of depression, anxiety or pain treated with eszopiclone for up to 8 weeks. It should be noted that the 1 mg dose in adults demonstrated inconsistent efficacy in improving sleep onset or nocturnal awakening measures and did not improve total sleep time in any study. Thus, the usual effective dose is expected to be 2 or 3 mg for adults.

Co-morbid insomnia

In subjects with insomnia together with depression or anxiety, coadministration of eszopiclone with a selective serotonin reuptake inhibitor (SSRI) for 8 weeks demonstrated significant improvements in sleep measures as well as certain clinically relevant measures of antidepressant and anxiolytic response (e.g., Hamilton Depression and Anxiety Rating scales) compared to administration of SSRI monotherapy. In 4-week studies of insomnia due to rheumatoid arthritis or perimenopausal symptoms, eszopiclone demonstrated significant improvements in sleep measures (sleep onset and sleep maintenance) for the study duration. In these studies, improvements in the perception of pain in subjects with rheumatoid arthritis and improvements in mood and menopause-related symptoms in perimenopausal and menopausal women treated with eszopiclone were also noted.

Elderly population

Exposure to eszopiclone is increased in elderly patients 65 years or older (see section 5.2) and a total daily dose of eszopiclone should not exceed 2 mg in the elderly. In randomised, double-blind, placebo-controlled studies in elderly patients with chronic insomnia up to 12 weeks duration, 2 mg eszopiclone once daily before bedtime demonstrated significant improvements in sleep measures (sleep onset and sleep maintenance) for the study duration.

Paediatric population

The licensing authority has deferred the obligation to submit the results of studies with eszopiclone in all subsets of the paediatric population in the treatment of insomnia. See section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Absorption
Eszopiclone is rapidly absorbed following oral administration. Peak plasma concentrations are achieved within 1 hour after oral administration.

Distribution
Eszopiclone is weakly bound to plasma protein (52-59%). Therefore, eszopiclone disposition is unlikely to 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.
In vitro studies have shown that CYP3A4 and CYP2E1 enzymes are involved in the metabolism of eszopiclone. Findings from *in vitro* studies of human hepatocytes with eszopiclone have shown that no inhibition of CYP450 1A2, 2A6, 2C9, 2C19, 2D6, 2E1 and 3A4 enzymes was observed. In humans,the exposure of eszopiclone was increased by approximately 2-fold by co-administration of ketokonazol 400 mg daily for 5 days, a potent inhibitor of CYP3A4. Other potent inhibitors of CYP3A4 (such as other azole antimycotics, macrolide antibiotics, grapefruit juice) would be expected to behave similarly. Conversely, potent inducers of CYP3A4 would be expected to reduce systemic exposure to eszopiclone.

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 parent drug.

Effect of food
In healthy adults, administration 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 at approximately 6 hours. The effects of eszopiclone on sleep onset may be slightly reduced if it is taken with or immediately after a high-fat or heavy meal.

Linearity/non-linearity
In healthy adults eszopiclone does not accumulate with once-daily administration and its exposure is dose-proportional in the range of 1 to 6 mg.

Special populations
Elderly
Compared with non-elderly adults, subjects 65 years and older had an increase of 41% in 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 of eszopiclone must not exceed 2 mg.

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

Ethnicity
The pharmacokinetics of eszopiclone in all ethnic groups studied appear similar (eszopiclone was studied in caucasian, black, hispanic, asian and other).

Hepatic impairment
Pharmacokinetics of a 2 mg dose were assessed in subjects with mild, moderate, and severe liver disease and compared to healthy volunteers. Exposure to eszopiclone was increased 2-fold in severely impaired patients compared with healthy volunteers. Observed maximum concentration (C_{max}) and its time of occurrence (t_{max}) were unchanged. Eszopiclone is contraindicated in patients with severe hepatic impairment. No dose adjustment is necessary for patients with mild-to-moderate hepatic impairment.

Renal impairment
The pharmacokinetics of eszopiclone were studied in subjects with mild, moderate or severe renal impairment. Compared with healthy subjects, subjects with severe renal impairment had an increase in exposure (AUC) of 47%. The maximum recommended dose of eszopiclone in patients with severe renal impairment is 2 mg. No dose adjustment is necessary in patients with mild or moderate renal impairment.

5.3 Preclinical safety data

Effects in nonclinical studies were observed only at exposures considered sufficiently in excess of the

maximum human exposure indicating little relevance to clinical use.

Genotoxicity and carcinogenicity

Eszopiclone and the pharmacologic active metabolite (S)-DMZ do not represent a mutagenic or carcinogenic risk in animal studies.

Reproductive and developmental toxicity

Eszopiclone was not teratogenic in repeat-dose toxicity studies and in reproductive and developmental studies conducted in mice, rats, rabbits and dogs, respectively. Eszopiclone and the pharmacologic active metabolite (S)-N-desmethyl zopiclone, showed degeneration of the male reproductive organs (testis, epididymides), reduced fertility indices in both genders, disruption of estrous cyclicity (rat) and acceleration of the time to onset of reproductive senescence (rat), at doses exceeding the maximum clinical dose (16 x for males and 13 x for females based on body surface area). All findings demonstrate reversibility after recovery.

Delays in foetal intrauterine development in rats and rabbits and reduced post-natal survival during the pre-weaning period in rats accompanied by maternal toxicity were observed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

cellulose, microcrystalline

calcium hydrogen phosphate

croscarmellose sodium

silica, colloidal anhydrous

magnesium stearate

Film-coating

hypromellose

talc

titanium dioxide (E171)

macrogol 3350

indigo carmine aluminium lake (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PVdC/PVC–Aluminium Blisters, PVC/PCTFE–Aluminium Blisters or OPA/ALU/PVC-Aluminium Blisters.

Pack sizes: 10, 14, 20 or 30 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

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Email: medinfo@axunio.de

8 MARKETING AUTHORISATION NUMBER(S)

PL 47848/0044

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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