



HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ESZOPICLONE TABLETS safely and effectively. See full prescribing ESZOPICLONE tablets, for oral use, CIV

Initial U.S. Approval: 2004

WARNING: COMPLEX SLEEP BEHAVIOUR

See full prescribing information for complete boxed warning. Complex sleep behaviors including sleep-walking, sleep-driving, and engaging in other activities while not fully awake may occur following use of eszopiclone tablets. Some of these events may result in ser rious injuries, including death. Discontinue eszopi tablets immediately if a patient experiences a complex sleep behavior (4, 5.1).

--- RECENT MAJOR CHANGES Boxed Warning 08/2019 Contraindications (4) 08/2019 Warnings and Precautions, Complex Sleep Behaviors (5.1) Warnings and Precautions, CNS Depressant Effects and Next-Day Impairment (5.2) 12/2018INDICATIONS AND USAGE...

Eszopiclone tablets are indicated for the treatment of insomnia. Eszopiclone tablets has been shown to decrease sleep latency and improve sleep

- -- DOSAGE AND ADMINISTRATION-Use the lowest dose effective for the patient (2)
- Recommended initial dose is 1 mg, immediately before bedtime, with at least 7 to 8 hours remaining before the planned time of awakening. May increase dose if clinically indicated, to a maximum of 3 mg (2.1) Geriatric or debilitated patients: Dose should not exceed 2 mg (2.2)
- Patients with severe hepatic impairment, or taking potent CYP3A4 inhibitors: Dose should not exceed 2 mg (2.3)
- Do not take with or immediately after a meal (2.5)

--- DOSAGE FORMS AND STRENGTHS --Tablets: 1 mg, 2 mg, and 3 mg (3)

FULL PRESCRIBING INFORMATION: CONTENTS* WARNING: COMPLEX SLEEP BEHAVIORS

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FULL PRESCRIBING INFORMATION

WARNING: COMPLEX SLEEP BEHAVIORS

Complex sleep behaviors including sleep-walking, sleep-driving, and engaging in other activities while not fully awake may occur following use of eszopiclone tablets. Some of these events may result in serious injuries, including death. Discontinue es tablets immediately if a patient experiences a complex sleep behavior (see Contraindications (4) and Warnings and Precautions (5.1)).

INDICATIONS AND USAGE bedtime decreased sleep latency and improved sleep maintenance.

The clinical trials performed in support of efficacy were up to 6 months in duration. The final formal assessments of sleep latency and maintenance were performed at 4 weeks in the 6-week study (adults only), at the end of both 2-week studies (elderly only) and at the end of the 6-month study (adults only).

2 DOSAGE AND ADMINISTRATION

2.1 Dosage in Adults

nded 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 o eszopiclone tablets 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 [see Warnings and Precautions (5.1/]. The total dose of eszopiclone tablets should not exceed 3 mg, once daily immediately before bedtime [see Warnings

2.2 Geriatric or Debilitated Patients

The total dose of eszopiclone tablets should not exceed 2 mg in elderly or debilitated patients. 2.3 Patients with Severe Hepatic Impairment, or Taking Potent CYP3A4 Inhibitors In patients with severe hepatic impairment, or in patients coad

szoniclone tablets with notent CYP3A4 inhibitors, the total dose of eszoniclon tablets should not exceed 2 mg [see Warnings and Precautions (5.7/]

Dosage adjustments may be necessary when eszopiclone tablets are combined with othercentral nervous system (CNS) depressant drugs because of the potentially additive effects (see Warnings and Precautions (5.1))

2.5 Administration with Food

Taking eszopiclone tablets with or immediately after a heavy, high-fat meal results in slower absorption and would be expected to reduce the effect of eszopiclone tablets on sleep latency/see Clinical Pharmacology (12.3).

DOSAGE FORMS AND STRENGTHS Eszopicione tablets, USP are available in 1 mg, 2 mg and 3 mg strengths for oral administration.

Eszopicione tablets USP, 3 mg are dark blue to blue, round, biconvex, film-coated tablets debossed with 'H' on one side and 'E16' on the other side

Eszopicione tablets USP, 2 mg are white to off-white, round, biconvex, film-coated tablets debossed with 'H' on one side and 'E15' on the other side. piclone tablets USP, 1 mg are light blue, round, biconvex, film-coated tablets debossed with 'H' on one side and 'E14' on the other si

CONTRAINDICATIONS Eszopiclone tablet is contraindicated in patients who have experienced complex sleep behaviors after taking eszopiclone tablets [see Warnings and Eszopiclone tablet is contraindicated in patients with known hypersensitivity to eszopiclone. Hypersensitivity reactions include anaphylaxis and

angioedema [see Warnings and Precautions (5.3)]. WARNINGS AND PRECAUTIONS

5.1 Complex Sleep Behaviors Complex sleep behaviors including sleep-walking, sleep-driving, and engaging in other activities while not fully awake may occur following the first or any subsequent use of eszopiclone tablet. Patients can be seriously injured or injure others during complex sleep behaviors. Such injuries may result in a fatal outcome. Other complex sleep behaviors (e.g., preparing and eating food, making phone calls, or having sex) have also been reported. Patients usually do not remember these events. Post-marketing reports have shown that complex sleep behaviors may occur with eszopiclone alone at recommended dosages, with or without the concomitant use of alcohol or other CNS depressants [see Drug Interactions (7.1)]. Discontinue eszopiclone immediately if a patient experiences a complex sleep behavior

5.2 CNS Depressant Effects and Next-Day Impairment Eszopicione tablet is a CNS depressant and can impair daytime function in some patients 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 pairment 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 tablets may develop, patients using 3 mg eszopiclone tablets 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 tablets and concomitant CNS depressants should be considered (see Dosage and Administration (2.4)]. The use of eszopic lone tablets 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 tablets are 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 coadministered with other drugs that increase the blood

evels of eszopiclone [see Dosage and Administration (2.3) and Clinical Studies (14.3)]. Because eszopiclone tablets can cause drowsiness and a decreased level of consciousness, patients, particularly the elderly, are at higher risk of falls. 5.3 Need to Evaluate for Comorbid Diagnoses Because sleep disturbances may be the presenting manifestation of a physical and/or psychiatric disorder, symptomatic treatment of instructions of the presenting manifestation of a physical and/or psychiatric disorder, symptomatic treatment of instructions of the presenting manifestation of the presenting manifestati

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 escopicione tablets. Because some of the important adverse effects of escopicione tablets appear to be dose related, it is important to use the lowest possible effective dose, especially in the elderly [see Dosage and Administration (2.1)].

5.4 Severe Anaphylactic and Anaphylactoid Reactions Rare cases of anginedema involving the tongue, glottis or larynx have been reported in patients after taking the first or subsequent doses of sedative-hypnotics, including eszopiclone tablets. 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,

ly obstruction may occur and be fatal. Patients who develop angioedema after treatment with eszopiclone tablets should not be rechallenged with the 5.5 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 change 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. It can rarely be determined with certainty whether a particular instance of the abnormal behaviors listed above is 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 5.6 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 [see Drug Abuse and Dependence (9)]. 5.7 Timing of Drug Administration

Eszopiclone Tablets 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.

5.8 Special Population

Use in Patients with Concomitant Illness

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 [see Dosage and Administration (2.2)].

Clinical experience with eszopiclone in patients with concomitant illness is limited. Eszopiclone tablets 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 tablets are prescribed to patients with compromised respiratory function. The dose of eszopiclone tablets 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 impair degree of renal impairment, since less than 10% of eszopiclone is excreted unchanged in the urine

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

Use in Patients with Depression

In primarily depressed patients treated with sedative-hypnotics, worsening of depression, including suicidal thoughts and actions (including completed suicides), have been reported in association with the use of sedative/hypr

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.

6 ADVERSE REACTIONS The following are described in more detail in the *Warnings and Precautions* section of the label

- Complex Sleep Behaviors (see Boxed Warning and Warnings and Precautions (5.1))
 CNS Depressant Effects and Next-Day Impairment (see Warnings and Precautions (5.2))
- Need to Evaluate for Comorbid Diagnoses (see Warnings and Precautions (5.3)) Severe Anaphylactic and Anaphylactoid Reactions [see Warnings and Precautions (5.4)]
- Abnormal Thinking and Behavioral Changes (see Warnings and Precautions (5.5)) Withdrawal Effects (see Warnings and Precautions (5.6))
- Timing of Drug Administration (see Warnings and Precautions (5, 7)) Special Populations (see Warnings and Precautions (5.8))
- Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly

compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. The premarketing development program for eszopiclone tablets 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 tablets varied greatly and included (in overlapping categories) open-label and double-blind phases of studies, inpatients and outpatients, and ure. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights

The stated frequencies of adverse reactions represent the proportion of individuals who experienced, at least once, adverse reaction 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

Patients who have experienced complex sleep behaviors after taking eszopiclone tablets (4)

Withdrawal Effects Symptoms may occur with rapid dose reduction or discontinuation (5.6, 9.3)

---WARNINGS AND PRECAUTIONS--CNS Depressant Effects Impaired alertness and motor coordination, including risk of morning impairment. Risk increases with dose and use with

- other CNS depressants and alcohol. Caution patients taking 3 mg dose against driving and against activities requiring complete mental alertness during the morning after use. (5.2) $\textit{Evaluate for Comborbid Diagnoses} \ \text{Reevaluate if insomnia persists after 7 to 10 days of use} \ (5.3)$
- Severe Anaphylactic/Anaphylactoid Reactions (angioedema and anaphylaxis have been reported): Do not rechallenge if such reactions occur (5.4) Abnormal Thinking amd Behavioral Changes Changes including decreased inhibition, bizarre behavior, agitation and depersonalization have been
- reported. Immediately evaluate any new onset of behavioral changes (5.5) $\textit{Worsening of Depression or Suicidal Thinking} \ \text{may occur: Prescribe the least number of tablets feasible to avoid intentional overdose} \ (5.5, 5.8)$
- Elderly Patients Use lower dose due to impaired motor, cognitive performance and increased sensitivity (2.2, 5.8) Patients with Hepatic Impairment, Impaired Respiratory Function, Impaired Drug Metabolism or Hemodynamic Responses Use with caution (5.8)ADVERSE REACTIONS..... $Most \ commonly \ observed \ adverse \ reactions \ (incidence \ge 2\%) \ were \ unpleasant \ taste, headache, somnolence, respiratory \ infection, \ dizziness, \ dry \ mouth \ discontinuous \$

rash, anxiety, hallucinations, and viral infections (6.1) To report SUSPECTED ADVERSE REACTIONS, contact Annora Pharma Private Limited at 1-866-495-1995 or FDA at 1-800-FDA-1088 o

- ----DRUG INTERACTIONS--- $\textit{CNS Depressants} \ Additive \ CNS - depressant \ effects \ with \ combination \ use. \ Use \ with \ ethanol \ causes \ additive \ psychomotor \ impairment \ (7.1)$ Rifampicin Combination use may decrease exposure and effects of eszopiclone tablets (7.2)
- Ketoconazole Combination use increases exposure and effect of eszopiclone tablets. Dose reduction of eszopiclone tablet is needed (7.2)USE IN SPECIFIC POPULATIONS

Pediatric Use Safety and effectiveness not established. Dizziness, dysgeusia, hallucinations, suicidal ideation reported (8.4) See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 01/2023

- 8.5 Geriatric Use 8.6 Hepatic Impairm 9 DRUG ABUSE AND DEPENDENCE
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8.4 Pediatric Use

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6.1 Clinical Trials Experience

Adverse Reactions Resulting in Discontinuation of Treatm 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 tablets, and 1.4% of 72 patients who received 1 mg eszopiclone tablets 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 placebo and 12.8% of 593 patients who received 3 mg eszopiclone tablets 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 $\geq 2\%$ in Controlled Trials

Table 1 shows the incidence of adverse reactions from a Phase 3 placebo-controlled study of eszopiclone tablets at doses of 2 or 3 mg in nonelderly adults Treatment duration in this trial was 44 days. The table includes only reactions that occurred in 2% or more of patients treated with escopicione tablets 2 mg $or 3\,mg in which the incidence in patients\ treated\ with\ eszopic lone\ was\ greater\ than\ the\ incidence\ in\ placebo-treated\ patients$

Table 1: Incidence (%) of Adverse Reactions in a 6-Week Placebo-Controlled Study in Nonelderly Adults with Eszopicione Tablets

Adverse Reaction	Placebo (n=99)	Eszopiclone tablets 2 mg (n=104)	Eszopiclone tablets 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

Reactions for which the eszopiclone tablets incidence was equal to or less than placebo are not listed on the table, but included the following: abnorma dreams, accidental injury, back pain, diarrhea, flu syndrome, myalgia, pain, pharyngitis, and rhinitis

* Gender-specific adverse reaction in females * Gender-specific adverse reaction in male

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

adults (ages 65 to 86). Treatment duration in these trials was 14 days. The table includes only reactions that occurred in 2% or more of patients treate with eszopiclone tablets 1 mg or 2 mg in which the incidence in patients treated with eszopiclone tablets was greater than the incidence in placebo-treate

Table 2: Incidence (%) of Adverse Reactions in Elderly Adults (Ages 65 to 86 Years) in 2-Week Placebo-Controlled Trials with Eszopiclone

Adverse Reactions	Placebo (n=208)	Eszopiclone tablets 1 mg (n=72)	Eszopiclone tablets 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

Reactions for which the eszopiclone tablets incidence was equal to or less than placebo are not listed on the table, but included the following: abdomi 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 othe

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 nondrug factors to the adverse reaction incidence rate in the population studied. Other Reactions Observed During the Premarketing Evaluation of Eszopiclone Tablets 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 mately 1550 subjects treated with eszopiclone tablets 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 labeling, minor reactions

tablets, 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 advers 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

mon in the general population, and reactions unlikely to be drug-related. Although the reactions reported occurred during treatmer

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

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

dysphagia, gastritis, hepatitis, hepatomegaly, liver damage, stomach ulcer, stomatitis, tongue edema, rectal hemorrhage Hemic and Lymphatic System: Infrequent: anemia, lymphadenopathy. Metabolic and Nutritional: Frequent: peripheral edema; Infrequent: hypercholesteremia, weight gain, weight loss; Rare: dehydration, gout, hyperlipemia

Musculoskeletal System: Infrequent: arthritis, bursitis, joint disorder (mainly swelling, stiffness, and pain), leg cramps, myasthenia, twitching; Rare Nervous System: Infrequent: agitation, apathy, ataxia, emotional lability, hostility, hypertonia, hypesthesia, incoordination, insomnia, memor osis, 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 discoloration, sweating, urticaria; Rare: erythema multiforme, furunculosis, hernes zoster, hirsutism, maculonanular rash, vesiculohullous rash, Special Senses: Infrequent: conjunctivitis, dry eyes, ear pain, otitis externa, otitis media, tinnitus, vestibular disorder; Rare: hyperacusis, iritis, mydriasis 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 hemorrhage, vaginal

6.2 Postmarketing Experience 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 postmarketing surveillance with eszopiclone tablets. Because this event is reported spontaneously from a popula unknown size, it is not possible to estimate the frequency of this event.

DRUG INTERACTIONS 7.1 CNS Active Drugs

nemorrhage, vaginitis; Rare: oliguria, pyelonephritis, urethritis

Ethanol: An additive effect on psychomotor performance was seen with coadministration of eszopiclone and ethanol /see Warnings and Precautions (5.1, 5.2)]. 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 7.2 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 coadministration 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 tablet is needed for patient co-administered eszopiclone tablets with potent CYP3A4

Read the Medication Guide that comes with eszopiclone tablets before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your doctor about your medical condition or treatment.

MEDICATION GUIDE

Eszopiclone Tablets, USP C-IV

(ess-ZOP-ih-klone)

What is the most important information I should know about eszopiclone tablets?

Do not take more eszopiclone tablets than prescribed.

- Do not take eszopiclone tablets unless you are able to stay in bed a full night (7 to 8 hours) before you must be active again.
- Take eszopiclone tablets right before you get in bed, not sooner.

Eszopiclone tablets may cause serious side effects, including:

Complex sleep behaviors that have caused serious injury and death. After taking eszopiclone tablets, you may get up out of bed while not being fully awake and do an activity that you do not know you are doing (complex sleep behaviors). The next morning, you may not remember that you did anything during the night. These activities may occur with eszopiclone tablets whether or not you drink alcohol or take other medicines that make you sleepy.

Reported activities and behaviors include:

- · doing activities when you are asleep like:
 - o making and eating food
 - o talking on the phone
 - o having sex
- o driving a car ("sleep-driving")

o sleep walking Stop taking eszopiclone tablets and call your healthcare provider right away if you find out that you have done any of the above activities after taking eszopiclone

The morning after you take eszopiclone tablets your ability to drive safely and think clearly may be decreased. You also may experience sleepiness during the day.

- Do not take eszopiclone tablets if you: have ever experienced a complex sleep behavior (such as driving a car, making and eating food, talking on the phone or having sex while not fully awake) after taking eszopiclone tablets.
- drank alcohol that evening or before bed

take other medicines that can make you sleepy. Talk to your doctor about all of your medicines. Your doctor will tell you if you can take eszopiclone tablets with your other cannot get a full night's sleep

Eszopiclone tablets are a sedative-hypnotic (sleep) medicine. Eszopiclone tablets are used in adults for the treatment of a sleep problem called insomnia. Symptoms of insomnia include: trouble falling asleep

WHAT ARE ESZOPICLONE TABLETS?

 waking up often during the night Eszopiclone tablets are not for children.

Eszopiclone tablets are a federally controlled substance (C-IV) because it can be abused or lead to dependence. Keep eszopiclone tablets in a safe place to prevent misuse and abuse. Selling or giving away eszopiclone tablets may harm others, and is against the law. Tell your doctor if you have ever abused or been dependent on alcohol, prescription medicines or street

Who should not take eszopiclone tablets?

- Do not take eszopiclone tablets if you have ever had a complex sleep behavior happen after taking eszopiclone tablets.
- Do not take eszopiclone tablets if you are allergic to anything in it. See the end of this Medication Guide for a complete list of ingredients in eszopiclone tablets.

Eszopiclone tablets may not be right for you. Before starting eszopiclone tablets, tell your doctor about all of your health conditions, including if you:

- have a history of depression, mental illness, or suicidal thoughts
- have a history of drug or alcohol abuse or addiction have liver disease are pregnant, planning to become pregnant, or breastfeeding

medicines, vitamins and herbal supplements. Medicines can interact with each other, sometimes causing serious side effects. Do not take eszopiclone tablets with other medicines that

Tell your doctor about all of the medicines you take including prescription and nonprescription

Know the medicines you take. Keep a list of your medicines with you to show your doctor and

pharmacist each time you get a new medicine. How should I take eszopiclone tablets?

before you must be active again.

- Take eszopiclone tablets exactly as prescribed. Do not take more eszopiclone tablets than prescribed for you.
- Do not take eszopiclone tablets with or right after a meal. • Do not take eszopiclone tablets unless you are able to get a full night's sleep
- Call your doctor if your insomnia worsens or is not better within 7 to 10 days. This may mean that there is another condition causing your sleep problems.

If you take too much eszopiclone tablets or overdose, call your doctor or poison control center right away, or get emergency treatment.

• Take eszopiclone tablets right before you get into bed.

What are the possible side effects of eszopiclone tablets? Possible serious side effects of eszopiclone tablets include:

- getting out of bed while not being fully awake and doing an activity that you do **not know you are doing.** (See "What is the most important information I should know
- about eszopiclone tablets?") abnormal thoughts and behavior. Symptoms include more outgoing or aggressive behavior than normal, confusion, agitation, acting strangely, hallucinations, worsening

• severe allergic reactions. Symptoms include swelling of the tongue or throat, trouble

of depression, and suicidal thoughts or actions. memory loss

anxiety

drowsiness

- breathing, and nausea and vomiting. Get emergency medical help if you get these symptoms after taking eszopiclone tablets.
- Call your doctor right away if you have any of the above side effects or any other side effects that worry you while using eszopiclone tablets.

· unpleasant taste in mouth, dry mouth

 dizziness headache

The most common side effects of eszopiclone tablets are:

 symptoms of the common cold You may still feel drowsy the next day after taking eszopiclone tablets. Do not drive or do other dangerous activities after taking eszopiclone tablets until you feel fully

These are not all the side effects of eszopiclone tablets. Ask your doctor or pharmacist for more information. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store eszopiclone tablets?

- Store eszopiclone tablets at 68°F to 77° F (20°C to 25° C). • Do not use eszopiclone tablets after the expiration date.
- General Information about eszopiclone tablets
- Do not share eszopiclone tablets with other people, even if you think they have the same symptoms that you have. It may harm them and is against the law.

This Medication Guide summarizes the most important information about eszopiclone tablets. If you would like more information, talk with your doctor. You can ask your doctor or

Size: 350 x 600 mm

Pharma Code: Front-227 & Back-228 Spec.: Printed on 40 GSM Bible paper, front & back side printing Note: Pharma code position and Orientation are tentative. will be changed based on folding size. No of Colours: 01 - Pantone Black C

• Keep eszopiclone tablets and all medicines out of reach of children.

• Medicines are sometimes prescribed for purposes other than those listed in a Medication

Do not use eszopiclone tablets for a condition for which it was not prescribed.

pharmacist for information about eszopiclone tablets that is written for healthcare professionals.

• For more information, call 1-866-495-1995.

What are the ingredients in eszopiclone tablets?

Active Ingredient: eszopiclone USP

Inactive Ingredients: calcium phosphate, colloidal silicon dioxide, croscarmellose sodium, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, titanium dioxide, and triacetin. In addition, both the 1 mg and 3 mg tablets contain FD&C Blue #2/indigo carmine aluminium lake.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Medication Guide available at http://camberpharma.com/medication-guides



Manufactured for: Camber Pharmaceuticals, Inc. Piscataway, NJ 08854

By: Annora Pharma Pyt. Ltd. Sangareddy - 502313, Telangana, India.

Revised: 01/2023

Drugs that Induce CYP3A4 (Rifampicin)

Racemic zopiclone exposure was decreased 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 tablet

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy Risk Summary

> Available pharmacovigilance data with escopicione use in pregnant women are insufficient to identify a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. In animal reproduction studies conducted in pregnant rats and rabbits throughout organogenesis, there was no evide of teratogenicity. Administration of eszopiclone to rats throughout pregnancy and lactation resulted in offspring toxicities at all doses tested; the lowest dose was approximately 200 times the maximum recommended human dose (MRHD) of 3 mg/day based on mg/m²body surface area *(See Data)* The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Animal Data

Oral administration of eszopicione 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 assification were observed at the mid and high doses. The no observed effect dose for adverse effects on embryofetal development is 200 times the nmended human dose (MRHD) of 3 mg/day on a mg/m² basis. No effects on embryofetal development were observed in rabbits; the highes dose tested is approximately 100 times the MRHD on a mg/m²basis.

Oral administration of eszopiclone (60, 120, or 180 mg/kg/day) to pregnant rats throughout the pregnancy and lactation resulted in increased postimplantation 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/m²basis. Eszopiclone had no effects on other develop

8.2 Lactation

Risk Summary There are no data on the presence of eszopiclone in either human or animal milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for eszopiclone and any potential adverse effects on the breastfed infant from eszopiclone or from the underlying maternal condition.

Safety and effectiveness of eszopiclone tablets have not been established in pediatric patients. Eszopiclone tablets failed to demonstrate efficacy in controlled clinical studies of pediatric patients with Attention-Deficit/Hyperactivity (ADHD)

In a 12-week controlled study, 483 pediatric patients (aged 6 to 17 years) with insomnia associated with ADHD (with 65% of the patients using concomitant ADHD treatments) were treated with oral tablets of eszopiclone (1, 2 or 3 mg tablets, n = 323), or placebo (n = 160). Eszopiclone did no 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 dyspeusia (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 (AUC) for eszopiclone and metabolite (S)-desmethylzopiclone [(S)-DMZ] approximately 2 times plasma exposures (AUC) for eszopiclone and metabolite (S)-desmethylzopiclone [(S)-DMZ] approximately 2 times plasma exposures (AUC) for eszopiclone and metabolite (S)-desmethylzopiclone [(S)-DMZ] approximately 2 times plasma exposures (AUC) for eszopiclone and metabolite (S)-desmethylzopiclone [(S)-DMZ] approximately 2 times plasma exposures (AUC) for eszopiclone and metabolite (S)-desmethylzopiclone [(S)-DMZ] approximately 2 times plasma exposures (AUC) for eszopiclone and metabolite (S)-desmethylzopiclone [(S)-DMZ] approximately 2 times plasma exposures (AUC) for eszopiclone and metabolite (S)-desmethylzopiclone [(S)-DMZ] approximately (S)-desmethylzopiclone [(S)-DMZ] appro humans at the 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 dose ≥ 10 mg/kg/day. The no-effect dose (1 ng/kg) was associated with plasma exposures (AUC) to eszopiclone and (S)-DMZ approximately 3 and 2 times, resp

8.5 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 tablets 2 mg exhibited significant reduction in sleep latency and improvement in sleep maintenance in the elderly population. Compared with nonelderly adults, subjects 65 years and older had longer elimination and higher total exposure to eszopiclone. Therefore, dose reduction is recommended in elderly patients (see Dosage and Administration (2.2), Clinical Pharmacology (12.3)].

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

used with caution in patients with hepatic impairment [see Dosage and Admin ration (2.3), Clinical Pharmacology (12.3)].

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Eszopiclone tablet is a Schedule IV controlled substance under the Controlled Substances Act. Other substances under the same classification are benzodiazepines and the nonbenzodiazepine hypnotics zaleplon and zolpidem. While eszopiclone is a hypnotic agent with a chemical structure unrelated to benzodiazepines, it shares some of the pharmacologic properties of the benzodiazepines

Abuse and addiction are separate and distinct from physical dependence and tolerance. Abuse is characterized by misuse of the drug for nonmedical purposes, often in combination with other psychoactive substances. Physical dependence is a state of adaptation that is manifested by a specific ithdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug and/or adminis antagonist. Tolerance is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time. Tolerance may occur to both the desired and undesired effects of drugs and may develop at different rates for different effects.

Addiction is a primary, chronic, neurobiological disease with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compu despite harm, and craving. Drug addiction is a treatable disease, utilizing a multidisciplinary approach, but relapse is common

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

The clinical trial experience with expenience tablets 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 substitutions and the complex control of the control of the

within 48 hours following the last escopicione tablets 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 eases 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 9.4 Tolerance

nnotic effect of henzodiazenines and henzodiazenine like agents may develon after reneated use of these drugs for a fev

No development of tolerance to any parameter of sleep measurement was observed over six months. Tolerance to the efficacy of eszopiclone tablets 3 mg was assessed by 4-week objective and 6-week subjective measurements of time to sleep onset and sleep maintenance for eszopiclone tablets in a placebo-con ments of time to sleep onset and wake time after sleep onset (WASO) in a placebo-controlled study for 6 months 44-day study, and by subjective asses 10 OVERDOSAGE

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 nations have recovered. Fatalities related to esconicione tablets overdoses were reported only in combination with other CNS drugs or alcohol.

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 postmarketing reports, most often associated with overdose with other CNSdepressant agents. Methemoglobinemia in association with overdoses of racemic zopiclone has been reported. 10.2 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. Consider monitoring methemoglobin in the setting of high-dose overdosage. 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

11 DESCRIPTION Eszopicione is a hypnotic agent/nonbenzodiazepine hypnotic agent that is a pyrrolopyrazine derivative of the cyclopyrrolone class. The chemical name of

oison control center for up-to-date information on the management of hypnotic drug product overdosage

eszopiclone is (+)4-Methyl-1-piperazinecarboxylic acid 6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5/pyrrol(3,4-b)pyrazin-5-(S)-yl ester. Its molecular weight is 388.81, and its molecular formula is C_0 H, CIN_aO_2 . Eszopiclone has a single chiral center with an (S)-configuration. It has the following chemical

 $Eszopiclone\ USP\ is\ a\ white\ to\ slight\ yellowish\ powder.\ Eszopiclone\ USP\ is\ soluble\ in\ methylene\ chloride\ and\ dilute\ hydrochloric\ acid;\ practically\ insoluble\ in\ methylene\ chloride\ and\ dilute\ hydrochloric\ acid;\ practically\ insoluble\ in\ methylene\ chloride\ and\ dilute\ hydrochloric\ acid;\ practically\ insoluble\ in\ methylene\ chloride\ and\ dilute\ hydrochloric\ acid;\ practically\ insoluble\ in\ methylene\ chloride\ and\ dilute\ hydrochloric\ acid;\ practically\ insoluble\ in\ methylene\ chloride\ and\ dilute\ hydrochloric\ acid;\ practically\ insoluble\ in\ methylene\ chloride\ acid\ practically\ insoluble\ in\ methylene\ chloride\ acid\ practical\ p$ Eszopiclone is formulated as film-coated tablets for oral administration, Eszopiclone tablets, USP contain 1 mg, 2 mg, or 3 mg eszopiclone USP and the

following inactive ingredients: anhydrous dibasic calcium phosphate, croscarmellose sodium, colloidal silicon dioxida, hypromellose lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, titanium dioxide, and triacetin. In addition, both the 1 mg and 3 mg tablets contain FD&C Blue #2/indigo carmine aluminium lake.

12 CLINICAL PHARMACOLOGY 12.1 Mechanism of action

12.3 Pharmacokinetics

The mechanism of action of eszopiclone as a hypnotic is unclear; however, its effect could be related to its interaction with GABA-receptor complexes at

The pharmacokinetics of escopicione have been investigated in healthy subjects (adult and elderly) and in 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,...) of approximately 1 hour and a terminal-phase elimination half-life (t₁₀) of

oximately 6 hours. In healthy adults, eszopiclone tablets does not accumulate with once daily administration, and its exposure is dose prop 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 to 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 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 After oral administration, eszopiclone is eliminated with a mean t, 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 C_{max} of 21%, and delayed t_{max} by approximately 1 hour The half-life remained unchanged, approximately 6 hours. The effects of eszopiclone tablets on sleep onset may be reduced if it is taken with or immediately

after a high-fat/heavy meal. Specific Population

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

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

Pharmacokinetics of a 2 mg eszopiclone dose were assessed in 16 healthy volunteers and in 8 subjects with mild, moderate, and severe liver disease

Exposure was increased 2-fold in severely impaired patients compared with the healthy volunteers. C., and L., 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. Eszopicione tablets should be used with caution in patients with hepatic impairment (see Dosage and Administration (2.3)). Renal Impairment The pharmacokinetics of eszopiclone were studied in 24 patients with mild, moderate, or severe renal impairment. AUC and Com, 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 parent drug. 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 zapine, but a pharmacodynamic interaction was seen on a measure of psychomotor function. Eszopiclone and lorazepa 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_m and t_{tr}, were increased 1.4-fold and 1.3-fold, respectively. Eszopiclone tablets would not be expected to alter the clearance of drugs metabolized by common CYP450 enzymes *[see Warnings and Precautions [5.7], Dosage and Administration [2.3]].*

Paroxetine: Coadministration of 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

Drugs with a Narrow Therapeutic Index x in the state of exponence x and x and x are the pharmacokinetics of dinoxin measured at steady state following dosing of 0.5 mg twice daily

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 ine is not highly bound to plasma proteins (52 to 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 drug that is highly protein bound would not be expected to cause an alteration in the free concentration of either drug

13 NONCLINICAL TOXICOLOGY

14 CLINICAL STUDIES

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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 eszopicione at the highest dose tested (16 mg/kg/day) are approximately 80 (females) and 20 (males) times those in humans at the MRHD of 3 mg/day. However, in a 2-year carcinogenicity study in rats, oral administration of racemic zopicione (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 ase in mammary adenocarcinomas is unknown. The increase in thyroid tumors is thought to be due to increased levels of TSH secondary to incre 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 nduced 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 of eszopiclone (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 in vivo chromosomal aberration and micronucleus assay

Impairment of Fertility oiclone to rats prior to and during mating, and continuing in females to day 7 of gestation (doses up to $45\,\mathrm{mg/kg/day}$ 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 ases 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/m²basis.

The effect of eszopicione tablets on reducing sleep latency and improving sleep maintenance was established in studies with 2100 subjects (ages 18 to 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 to 3 mg) and elderly dose (1 to 2 mg), eszopiclone tablets 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 tin

14.1 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 placebo. Eszopiclone tablets 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.

14.2 Chronic Insomnia (Adults and Elderly) The effectiveness of eszopiclone tablets was established in five controlled studies in chronic insomnia. Three controlled studies were in adult subjects, and two controlled studies were in elderly subjects with chronic insomnia

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 tablets 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 tablets 3 mg with placebo administered nightly for 6 months. Eszopiclone tablets was superior to placebo on subjective

measures of sleep latency, total sleep time, and WASO. In addition, a 6-period crossover PSG study evaluating eszopiclone doses of 1 to 3 mg, each given over a 2-day period, demonstrated effectiveness of all

doses on LPS, and of 3 mg on WASO. In this trial, the response was dose related Elderly subjects (ages 65 to 86 years) 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 tablets 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 tablets with placebo, while the second study compared 2 mg of eszopiclone tablets with placebo. All doses were superior to placebo on measures of sleep latency. In both studies, 2 mg of eszopiclone tablets was superior to placebo

14.3 Studies Pertinent to Safety Concerns for Sedative Hypnotic Drugs

Next-Day Residual Effects

In a double-blind study of 91 healthy adults age 25-to 40 years, the effects of eszopiclone tablets 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 ability to maintain a motor vehicle in the driving lane, tests of working memory, and subjective perception of sedation and coordination. Compared with placebo, eszopiclone tablets 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 tablets 3 mg was not consistently different from plac even though subjects were objectively impaired.

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

In a 2-week study of 264 elderly insomniacs, 1.5% of patients treated with eszopiclone tablets 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 tablets 2 mg reported confu 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, it is possible that 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 day time anxiety. In a 6-month double-blind, placebo-controlled study of nightly administration of eszopiclone tablets 3 mg, rates of anxiety reported as an adverse event were 2.1% in the placebo arm and 3.7% in the eszopiclone tablets 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, single-blind placebo was administered on nights 45 and 46, the first and second days of withdrawal from study drug. New adverse events were recorded during the withdrawal period, beginning with day 45, up to 14 days after discontinuation. During this withdrawal period, 105 subjects previously taking nightly eszopicione tablets 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

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 tablets 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 tablets 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 tablets 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 right of discontinuation. Comparisons of changes from baseline between eszopiclone tablets and placebo were also performed. On the first night after discontinuation of eszopiclone tablets 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 tablets 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 tablets discontinua

16 HOW SUPPLIED/STORAGE AND HANDLING Eszopiclone tablets USP, 3 mg are dark blue to blue, round, biconvex, film-coated tablets debossed with 'H' on one side and 'E16' on the other side

Bottles of 30 tablets NDC 31722-857-30 Eszopiclone tablets USP, 2 mg are white to off-white, round, biconvex, film-coated tablets debossed with 'H' on one side and 'E15' on the other side.

NDC 31722-856-30 Bottles of 30 tablets

Eszopiclone tablets USP, 1 mg are light blue, round, biconvex, film-coated tablets debossed with 'H' on one side and 'E14' on the other side. Bottles of 30 tablets NDC 31722-855-30

Store at 20° to 25° C (68° to 77° F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION See FDA-approved patient labeling (Medication Gu

Inform patients and their families about the benefits and risks of treatment with eszopiclone tablets. Inform patients of the availability of a Medication Guide and instruct them to read the Medication Guide prior to initiating treatment with eszopiclone tablets and with each prescription refill. Review the eszopiclone tablets Medication Guide with every patient prior to initiation of treatment. Instruct patients or caregivers that eszopiclone tablets should be taken only as prescribed. Complex Sleep Behaviors

Instruct patients and their families that ESZOPICLONE TABLETS may cause complex sleep behaviors, including sleep-walking, sleep-driving, preparing and eating food, making phone calls, or having sex while not being fully awake. Serious injuries and death have occurred during complex sleep behave Tell patients to discontinue ESZOPICLONE TABLETS and notify their healthcare provider immediately if they develop any of these symptoms (see Boxed Warning, Warnings and Precautions (5.1)].

CNS Depressant Effects and Next-Day Impairment

Severe Anaphylactic and Anaphylactoid Reactions

Tell patients that eszopiclone tablets can cause next-day impairment even when used as prescribed, and that this risk is increased if dosing instructions are not carefully followed. Caution patients taking the 3 mg dose against driving and other activities requiring complete mental alertness the day after use. Inform patients that impairment can be present despite feeling fully awake. Advise patients that increased drowsiness and decreased consci increase the risk of falls in some patients [see Warnings and Precautions (5.2)].

 $Inform \ patients\ that\ severe\ an aphylactic\ and\ an aphylactoid\ reactions\ have\ occurred\ with\ eszopic lone.\ Describe\ the\ signs/symptoms\ of\ these\ reactions\ and\ severe\ an aphylactoid\ reactions\ have\ occurred\ with\ eszopic lone.\ Describe\ the\ signs/symptoms\ of\ these\ reactions\ and\ severe\ have\ occurred\ with\ eszopic lone.$ advise patients to seek medical attention immediately if any of them occur [see Warnings and Precautions (5.4]].

Alcohol and Other Drugs

Ask patients about alcohol consumption, medicines they are taking, and drugs they may be taking without a prescription. Advise patients not to use Tolerance, Abuse, and Dependence

Tell patients not to increase the dose of eszopiclone tablets on their own, and to inform you if they believe the drug "does not work."

Patients should be counseled to take eszopiclone tablets right before they get into bed and only when they are able to stay in bed a full night (7 to 8 hours) before being active again. Eszopiclone tablets should not be taken with or immediately after a meal. Advise patients NOT to take eszopiclone tablets if they

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