# S-Clon®

... a single complete therapy to
treat transient & chronic insomnia

BEXIMCO PHARMA

BEXIMCO PHARMACEUTICALS LIMITED

# INSOMNIA & TREATMENT OPTIONS

**Eszopiclone (S-Clon):**
**a new nonbenzodiazepine hypnotic agent**

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# PART I: INSOMNIA

## About insomnia

**What is insomnia?**

Insomnia, defined as trouble falling asleep or staying asleep, is a common problem. Occasional insomnia is experienced by more than a third of American adults, and chronic insomnia is known to effect more than one in ten. If you have ever suffered from insomnia, you know it can disturb your waking, as well as your sleeping hours. It can cause you to feel sleepy or fatigued during the day, affect your mood and results in trouble focusing on tasks. Looking at both the daytime and the nighttime factors of insomnia can help individuals and their healthcare professional understand the causes of this condition, and provide a basis for treating the disorder. Recent research into psychological, lifestyle, environmental, physical and psychiatric factors behind sleep disorders is making it possible for healthcare professionals to help most troubled sleepers.

**Types of insomnia**

Insomnia can occur in people of all ages. Most individuals just experience a night or two of poor sleep, but sometimes the sleep disturbance can last for weeks, months, or even years. Insomnia is most common among women and older adults.

*Transient Insomnia*

Transient insomnia is the inability to sleep well over a period, lasting fewer than four weeks. This type of insomnia is usually brought on by excitement or stress. Children, for example, may toss and turn just before school starts, or before an important exam or sporting event. Adults might sleep poorly before an important business meeting or after an argument with a family member or close friend. People are more likely to have trouble sleeping when they are away from home, especially if they have

traveled across time zones. Physical activity close to bedtime (within four hours) and illness can also cause this type of insomnia.

*Short-term Insomnia*
Short-term insomnia is the inability to sleep well for a period of four weeks to six months. Periods of ongoing stress at work or at home, medical conditions, psychiatric illness or other persistent factors can result in short-term insomnia. As the cause resolves or the sleeper adjusts to it, sleep will usually return to normal.

*Chronic Insomnia*
More than 20 million Americans complain of chronic insomnia, defined as poor sleep every night or most nights for more than six months. While most of these individuals worry about their sleep, it's wrong to blame all troubled sleep on worrying. Insomnia may be a physical problem, not due to psychological factors. According to a nationwide study by the Association of Sleep Disorders Centers, physical ailments -such as disorders of breathing or abnormal muscle activity are often the cause of sleep disruption and may account for a large number of self-diagnosed cases of insomnia.

## Causes of Insomnia

**What causes insomnia?**
Insomnia may be independent of other healthcare problems. However, it also may be a symptom of another problem, much like a fever or a stomachache. It can be caused by a number of factors.

**Psychological Factors**

*Vulnerability to insomnia*
Some people seem more likely than others to experience insomnia, just as some people tend to get headaches or upset stomachs. Simply knowing that you may experience insomnia and that it will not last too long can be helpful in dealing with it when it occurs.

*Persistent stress*
Exposure to stress may contribute to the development or worsening of insomnia. Relationship problems, a chronically ill child, or an unrewarding career may contribute to sleep problems. If you suffer from these types of stresses, you should seek counseling to gain a new outlook on your troubles and more control in your life.

*Learned insomnia (also known as psychophysiological insomnia)*
If you sleep poorly, you may worry about not being able to function well during the day. You may try harder to sleep at night, but unfortunately this determined effort can make you more alert, set off a new round of worried thoughts, and cause more sleep loss. Doing activities in and around the bedroom-changing into your night clothes, turning off the lights, pulling up the blankets-can become linked with the sleep problems that follow. Through repetition these bedtime activities can then trigger over-arousal and insomnia. Some individuals with learned insomnia have trouble sleeping in their own beds yet may fall asleep quickly when they don't intend to-while reading the newspaper, sleeping away from home, or watching TV. Just a few nights of poor sleep during a month can be enough to produce a cycle of poor sleep and increase your worry about it. Treatment for learned insomnia aims to improve sleep habits and reduce unnecessary worry.

## Lifestyle Factors

*Use of stimulants*
Caffeine near bedtime, even when it doesn't interfere with falling asleep, can trigger awakenings later in the night. Nicotine is also a stimulant, and smokers may take longer to fall asleep than non-smokers. Be aware that the ingredients in many common drugs, including nonprescription drugs for weight loss, asthma and colds, can disrupt sleep.

*Use of alcohol*
Alcohol consumption is likely to produce interrupted sleep beginning a few hours after falling asleep.

*Erratic hours*
If you do shift work, or maintain later hours on weekends than during the week, you are more likely to experience sleep problems. Maintaining regular hours can help program your body to sleep at certain times and to stay awake at others. Establishing a routine is important.

*Inactive behavior*
People whose lifestyles are very quiet or restricted may experience difficulty sleeping at night.

**Environmental Factors**

*Noise*
Traffic, airplanes, television, and other noises can disturb sleep even when they don't cause the individual to wake up.

*Light*
Exposure to bright light prior to sleep can delay sleep onset, while light entering the bedroom can shorten sleep.

All of these environmental factors should be considered if you find yourself feeling tired, even when you think you slept soundly all night.

## Illness and Secondary Insomnia

Other sleep disorders, psychiatric and physical illnesses may disrupt sleep, and produce symptoms that can easily be mistaken for insomnia. These other disorders require medical attention and common treatments for insomnia alone will not help.

When insomnia is caused by a psychiatric disorder (most often depression) or a medical disorder (most often chronic pain), it is termed secondary insomnia. Secondary insomnia may be relieved by successful treatment of the primary psychiatric/medical disorder. Additionally, behavioral methods that target the sleep disturbance itself and may quite beneficial especially if some sleep disruption remains after effective treatment of the underlying disorder.

*Psychiatric problems*

Insomnia, especially with awakenings earlier than desired, is one of the most frequently reported symptoms of depression. Insomnia is also associated with anxiety disorders, post-traumatic stress disorders, and other conditions. Treatment of the underlying disorder, often including both medication and psychotherapy, can help improve your sleep.

*Medical problems*

Medical illnesses can disrupt sleep and produce symptoms of insomnia. For example, arthritis, headaches, benign prostatic hypertrophy, and other conditions can cause or worsen the problem of insomnia. Such medical problems usually require the attention of a physician who can diagnose and treat the underlying condition. Treatment of the underlying cause will result in improved sleep. However, in some cases specific treatment for insomnia also will be needed.

*Sleep-related breathing disorders*

Sleep-related breathing disorders such as sleep apnea can cause repeated pauses in breathing during sleep. This can wake a sleeper dozens or even hundreds of times during the night. Pauses in breathing can be as short as 10 seconds and may not be remembered in the morning. However, they are sufficient to produce disturbed and restless sleep. Severely disrupted breathing during sleep may affect people who breathe normally while they are awake. Breathing-related sleep problems are most common in

men, snorers, overweight people, and older adults. Loud snoring that is interrupted by gasps, snorts or other unusual sounds may be a warning sign of a sleep-related breathing disorder.

*Sleep-related periodic leg movements*

Brief muscle contractions can cause leg jerks that last a second or two and occur repeatedly about every 20-40 seconds for varying periods of time throughout the night (often for an hour or longer). In almost all cases the individual is totally unaware of the limb movements. These movements can cause hundreds of brief interruptions of sleep each night, resulting in restless or non-restorative sleep. Periodic limb movements become more frequent and severe as we grow older. Treatment can include medication, discontinuing medication, evening exercise, a warm bath, elimination of caffeine or a combination of these. Iron replacement may be helpful if there is an iron deficiency, especially if restless legs are also present.

*Waking brain activity*

Waking brain activity can persist during sleep. Sleep monitoring during the night has shown that some people who complain of light or less restful sleep show waking brain (EEG) activity occurring simultaneously with sleep activity. Individuals with persistent pain may experience this non-restorative type of sleep.

Gastroesophageal reflux

Back-up of stomach contents into the esophagus can awaken a person several times a night. This reflux is commonly known as heartburn because of the pain or tightness it produces in the mid-chest area. When reflux occurs during the day, a few swallows and an upright position will usually clear the irritating materials from the esophagus. During sleep, less-frequent swallowing and a lying-down position causes more reflux, making the sleeper wake up coughing and choking. Elevating the head or raising the head of the bed (headboard) onto 6- to 8-inch blocks may help. Medications can also provide relief.

# Treatment of Insomnia

## Sedative-Hypnotic Medications

These are medications approved by the FDA for use in the treatment of insomnia in USA. There are now five benzodiazepine compounds and three non-benzodiazepine compounds approved for use. It has been estimated that 2.5% of the population will take a hypnotic for insomnia within a given year. In addition to these prescription medications there are non-prescription hypnotics available over the counter, along with other medications (including a variety of antidepressants) that may be given by physicians to their patients to aid in either the onset or maintenance of sleep.

Use of medications must take into account not only nighttime problems but the daytime consequences of poor sleep. An accurate diagnosis must be the first goal. Is the insomnia secondary to a medical condition or depression? Is it related to transient stressors either at home or at the workplace? Does the patient have pets that are in the bedroom and may be contributing to disrupted sleep? These are just a few of the questions that your physician will need to address before deciding on whether or not medications are indicated for treatment.

## Benzodiazepine Hypnotics

The benzodiazepine medications are thought to work through their actions at a specific neurotransmitter receptor site (part of the GABA receptor complex). These hypnotic medications are all rapidly absorbed after being administered. They differ in their speed of action as well as the length of time that they are active. For example, one of the medications, triazolam has a very rapid onset of action and is also out of the system quickly. Other agents, such as flurazepam, have a much longer duration of action and have metabolites that may cause next-day drowsiness for some patients. The physician must decide which of the available

medications in this class would be the right choice for an individual based on complaints of onset, maintenance or early morning awakening insomnia. This group of medications does have the potential of being habit forming and is best avoided in patients known to have a history of substance abuse or dependence. Below is a table of the benzodiazepine agents and their dosage that are currently approved for use as hypnotics in USA.

| Generic name | Half life | Dosage |
|---|---|---|
| Flurazepam | 48-120 hours | 15-30mg |
| Quazepam | 48-120 hours | 7.5-15mg |
| Triazolam | 2-6 hours | 125-.25mg |
| Estazolam | 8-24 hours | 1-2mg |
| Temazepam | 8-20 hours | 15-30mg |

**Non-Benzodiazepine Hypnotic Medications**

There are now three medications in this class approved by the FDA in the treatment of insomnia. These agents are thought to work through their action on one of the subtypes of the GABA-benzodiazepine receptors. All three of these medications have been found to be safe and effective in the treatment of insomnia. They differ primarily in their duration of action. Once again, it is important to determine whether difficulty with initiation of sleep, sleep maintenance, or perhaps both, is the primary complaint. As you would expect, all of these medications have been shown through research to improve sleep quality. They are thought to be safe, and the newest of the medications (eszopiclone) has proven to be effective for nightly use over duration of six months. Below is a table of the half-life and dosages for these medications.

| Generic Name | Half life | Dosage |
|---|---|---|
| Zolpidem tartrate | 1.5-2.4 hours | 5-10mg |
| Zaleplon | 1 hour | 5-10mg |
| Eszopiclone | 5-7 hours | 1-3mg |

## Over-the-Counter (OTC) Medications

Many of the common over-the-counter medications used to induce sleep contain antihistamine agents. These agents are sedating, but they also have significant side effects. The main concern with these drugs involves next-day effects. Studies that have evaluated psychomotor skills, visual processing and even driving performance have confirmed that many of the commonly used antihistamine agents can cause impairment. In addition, adverse effects can include dry mouth, dry eyes, confusion and urinary retention.

## Sedating Antidepressants

Sometimes physicians will use sedating antidepressants to help patients with a variety of problems, including, but not restricted to depression. Medications in this class include amitriptyline, nortriptyline, doxepine and trazodone. For some patients, sleepiness in the daytime may be a problem, but these effects tend to diminish over time. In some patients the medications may actually worsen problems such as periodic limb movement disorder. In patients with fibromyalgia, however, sedating antidepressants may decrease pain. In patients whose insomnia is secondary to depression or anxiety, there will be improvement of sleep as the underlying mood or anxiety disorders improve.

## "Natural", Herbal and Other Home Remedies

"Natural," Herbal, and Other Home Remedies have been used for years. One of the most recent "natural" remedies for insomnia has been melatonin, which can be obtained at most health food stores. Melatonin is a hormone that is known to be involved in the regulation of sleep and wakefulness. It has been shown that the ingestion of melatonin prior to bedtime will help individuals fall asleep. However, scientific data have failed to confirm that melatonin is useful in maintaining sleep.

### A Combined Approach

Treatment of insomnia can be complicated; it usually involves not only pharmacotherapy, but also non-pharmacologic treatment. This non-pharmacologic treatment usually includes a reduction or elimination of caffeine and alcohol use, improved eating habits, establishing an exercise routine and keeping a relaxing bedtime routine. Your physician may ask you to log your sleep for several weeks to get a sense of your routine and to see where you are having the most difficulty. An approach that takes into account not only medications but sleep habits as well is much more likely to be effective.

## Frequently Asked Questions

**Are sleep medications dangerous or addictive?**
Modern day sleep medications are not dangerous when used as prescribed. The addictive potential of the newest classes of medication is believed to be low.

**When can sleep medications be used?**
Sleep medications can be used on a periodic basis, when needed to combat insomnia. Many people experience insomnia only a few times per year or per month. It is appropriate to use the medication in this way, provided that your doctor has recommended it.

Sleep medications also may be used on a nightly basis. Current prescription guidelines indicate that sleep medications should be used on a continuous basis for a limited period of time (a few weeks). However, data show that some people use the medication for longer periods. These people may have chronic problems with insomnia that require chronic treatments.

Most sleep medications need to be taken just before bedtime or at bedtime. This is due to the persistence of their effects over the course of the night. Some sleep medications may be able to be taken after bedtime, in response to symptoms or awakenings.

**Are sleep medications better than non-drug therapies for insomnia?**

No single therapy is better than any other. Since insomnia often arises from a variety of causes, and different people have different desires and attitudes regarding medication, it is hard to say that "one size fits all" with regard to insomnia treatment. It is most important that patients talk to their doctors about their problems, what they hope for with treatment and assess progress along the way.

**How long can I use the pills?**

Some people will use a sleeping pill for one night. Others may need long-term use of the medication on a nightly basis. If you use sleep medications over the long-term, it is important to maintain regular contact with your physician to determine the need for continued use and explore all of the options open to you. For example, in some cases a persistent problem with insomnia is a sign that other, underlying sleep problems exist. These need to be diagnosed and treated in order to find real relief.

**Will I be able to stop taking pills after I start?**

Yes. Newer sleep medications can be discontinued in a matter of a day or two, usually without withdrawal effects. Benzodiazepines may require a longer period of "tapering" before they actually can be discontinued. However, if managed properly, the discontinuation can be tolerated comfortably.

Always speak to your physician prior to discontinuing prescribed medication.

# PART II: ESZOPICLONE (S-Clon) : A new non-benzodiazepine hypnotic agent

## ABSTRACT

Randomized, placebo-controlled trials have shown that eszopiclone, a newly available nonbenzodiazepine hypnotic, effectively treats the symptoms of insomnia. Its pharmacokinetic and pharmacodynamic parameters are similar to those of the other currently available nonbenzodiazepine hypnotics (i.e., zolpidem and zaleplon). The unique quality of eszopiclone lies in its product labeling. It is not restricted to short-term use, unlike both zolpidem and zaleplon. Dosing of eszopiclone should begin at 2 mg for nonelderly patients and may be initiated at or increased to 3 mg if clinically indicated. The 3-mg nightly dose is more effective at sleep maintenance. Eszopiclone is well tolerated, with the main treatment-emergent side effects being unpleasant taste, headache, and dizziness.

The complaint of insomnia is defined as the perception of inadequate or nonrestorative sleep often related to difficulty initiating sleep, difficulty maintaining sleep, or frequent awakenings. It is typically classified as being either transient or chronic depending on the duration of a patient's symptoms. Transient insomnia, lasting only a few days, is often a result of acute stress, acute medical illness, jet lag or self-medication. Insomnia lasting longer than 3 weeks is considered chronic and is usually multifactorial, resulting from chronic anxiety, depression, alcohol or substance abuse or withdrawal, medication use, or age-related changes in sleep. In hospitalized patients, additional factors contribute to poor sleep quality, including the anxiety associated with physical illness, nocturnal isolation from family members and the disruptive effects of light, sounds and procedures in the hospital.

Poor nocturnal sleep quality can have a deleterious impact upon patient comfort, mood, and ability to cooperate with hospital procedures. Therefore, ensuring adequate sleep quality within the hospital environment is a vital component of good patient care. Treatment of insomnia in hospitalized patients usually consists of both nonpharmacologic and pharmacologic approaches. Nonpharmacologic measures typically focus on treatment of the underlying factor(s) contributing to a patient's insomnia and may include, for example, establishing a regular schedule of sleeping and waking times. Pharmacologic treatment consists of the short-term use of hypnotic agents, such as benzodiazepines (e.g., temazepam, lorazepam, estazolam), benzodiazepine omega-1 receptor agonists (e.g., zolpidem and zaleplon), and trazodone. Other agents with sedative properties, such as antihistamines (e.g., diphenhydramine) and atypical antipsychotics (e.g., quetiapine), have also been used as pharmacological therapy for insomnia. The choice of agent should be based on pharmacokinetic and pharmacodynamic properties of the medication as well as patient-specific characteristics.

The Food and Drug Administration (FDA) approved oral eszopiclone on December 15, 2004. It is the S-isomer of zopiclone, which has been available in Europe since 1992. Eszopiclone is the first of several new agents entering the US market for the treatment of insomnia. Other recently approved agents include the melatonin receptor agonist ramelteon and extended-release zolpidem.

## INDICATION

Eszopiclone is indicated for the treatment of transient and chronic insomnia in patients =18 years of age. Unlike other nonbenzodiazepine agents, there is no restriction on its duration of use.

## PHARMACOLOGY

The precise mechanism of action of eszopiclone as a hypnotic is unknown, but its effect is believed to result from its interaction with GABA receptor complexes at binding domains located close to or allosterically coupled to benzodiazepine receptors. Eszopiclone is a nonbenzodiazepine hypnotic that is structurally unrelated to pyrazolopyrimidines, imidazopyridines, benzodiazepines, barbiturates, or other drugs with known hypnotic properties.

## PHARMACOKINETICS

**Onset of action**
In a study conducted by Zammit et al in adults with chronic insomnia, the average onset of sleep (measured by sleep latency) was 10.4 minutes faster in the eszopiclone 2 mg group than in the placebo group.

**Absorption and distribution**
Eszopiclone is rapidly absorbed following oral administration. Peak plasma concentrations are achieved within 1 hour after oral administration. It is weakly bound to plasma proteins (52%-59%).

**Metabolism**
Following oral administration, eszopiclone is extensively metabolized in the liver by oxidation and demethylation. The primary plasma metabolites have little to no binding potency to GABA receptors. In vitro studies have shown that CYP3A4 and CYP2E1 enzymes are involved in the metabolism of eszopiclone.

**Elimination**
The mean elimination half-life ($t_{1/2}$) of eszopiclone is approximately 6 hours. Less than 10% of an oral 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 area under the curve (AUC), a 21% reduction in peak concentration (Cmax), and a 1-hour delayed time to reach peak concentration (tmax). The $t_{1/2}$ remained unchanged.

## ADVERSE EFFECTS

The two most frequent adverse events in both treatment durations were headache and unpleasant taste. Dyspepsia, pain, and diarrhea were also common in elderly patients treated for 14 days, whereas somnolence, dry mouth, and nausea were common in adults treated for 44 days.

## WARNINGS/PRECAUTIONS

While there are no known contraindications to eszopiclone, the drug should be administered with caution in patients exhibiting signs and symptoms of depression. Suicidal tendencies may be present, and intentional overdose is more common in such patients. Therefore, the smallest dose feasible should be prescribed to the patient. In clinical trials with eszopiclone, one case of overdose with up to 36 mg was reported in which the subject fully recovered.

In healthy volunteers, a 7-mg oral dose of eszopiclone did not produce respiratory-depressant effects. However, caution should be exercised in administration of eszopiclone to patients with compromised respiratory function.

*Tolerance may develop after repeated use of benzodiazepines and benzodiazepine-like agents for a few weeks. However, no evidence of developed tolerance was seen with eszopiclone over a period of 6 months in clinical trials.*

## DOSING AND ADMINISTRATION

The recommended starting dose for eszopiclone for most nonelderly adults is 2 mg immediately before bedtime. Dosing can be initiated at or raised to 3 mg if clinically indicated, since 3 mg is more effective for sleep maintenance.
Taking eszopiclone with or immediately after a heavy, high-fat meal results in slower absorption and would be expected to reduce the effect of eszopiclone on sleep latency.

**Dosing in special populations**
The elderly: The recommended starting dose for elderly patients whose primary complaint is difficulty falling asleep is 1 mg immediately before bedtime. The dose may be increased to 2 mg if clinically indicated. For elderly patients whose primary complaint is difficulty staying asleep, the recommended dose is 2 mg immediately before bedtime.

Hepatic impairment: The starting dose should be 1 mg in patients with severe hepatic impairment. Eszopiclone should be used with caution in these patients.

Renal impairment: No dose adjustments are necessary in patients with any degree of renal insufficiency.

**Pregnancy/lactation**
Pregnancy category C: There are no adequate, well-controlled studies of eszopiclone in pregnant women. Eszopiclone should be used during pregnancy only if the potential benefits outweigh the potential risks.

It is not known whether eszopiclone is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when eszopiclone is administered to a nursing mother.

## DRUG INTERACTIONS

### CNS-active drugs

Ethanol: An additive impairment of psychomotor performance was seen with coadministration of eszopiclone and ethanol.

Paroxetine: Coadministration of single doses of eszopiclone 3 mg and paroxetine 20 mg daily for 7 days produced no pharmacokinetic or pharmacodynamic interaction.

Lorazepam: Coadministration of single doses of eszopiclone 3 mg and lorazepam 2 mg did not have clinically relevant effects on the pharmacokinetics or pharmacodynamics of either drug.

Olanzapine: Coadministration of single doses of eszopiclone 3 mg and olanzapine 10 mg produced a decrease in DSST scores, resulting from a pharmacodynamic interaction. The pharmacokinetics of both drugs were unaltered. No specific recommendation for dose adjustments of either drug is made by the manufacturer in the prescribing information.

### Drugs that inhibit CYP3A4

The AUC of eszopiclone was increased 2- to 3-fold by co-administration of ketoconazole, a potent inhibitor of CYP3A4, 400 mg daily for 5 days. Cmax and tmax were increased 1.4-fold and 1.3-fold, respectively. Other strong inhibitors of CYP3A4 (e.g., itraconazole, clarithromycin, nefazodone, ritonavir, nelfinavir) would be expected to behave similarly. However, no specific recommendations for dose adjustments are made in the prescribing information.

### Drugs highly bound to plasma proteins

Eszopiclone is not highly bound to plasma proteins; 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 alter the free concentration of either drug.

**Drugs with a narrow therapeutic index**
Digoxin: A single dose of eszopiclone 3 mg did not affect the pharmacokinetics of digoxin measured at steady state.

Warfarin: Eszopiclone 3 mg administered daily for 5 days did not affect the pharmacokinetics of warfarin, nor were there any changes in prothrombin time following a single 25-mg oral dose of warfarin.

## PACKAGING

**S-Clon 1:** Box containing 6 blister strips of 10's tablets. Each tablet contains Eszopiclone INN 1 mg. **S-Clon 2:** Box containing 3 blister strips of 10's tablets. Each tablet contains Eszopiclone INN 2 mg.

## PART III: Clinical trial summary

This section summarizes the published clinical trials in Pubmed on the safety and efficacy of eszopiclone for the treatment of insomnia.

## A 2-weeks efficacy and safety study of eszopiclone in elderly patients with primary insomnia

**STUDY OBJECTIVES:** Evaluate the efficacy of eszopiclone in primary insomnia. **DESIGN/SETTING:** Randomized, double-blind, placebo-controlled multicenter in outpatient setting with weekly visits. **PARTICIPANTS:** Two-hundred thirty one men and women aged 65 to 85 years (mean age 72.3 years) with primary insomnia, as defined by the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition. **INTERVENTIONS:** Eszopiclone 1 mg (n = 72), eszopiclone 2 mg (n = 79), or placebo (n = 80) nightly for 2 weeks. **MEASUREMENTS/RESULTS:** Efficacy was assessed using an interactive voice response system. Following the predefined hierarchical testing strategy, the eszopiclone 2-mg group had a significantly shorter sleep latency compared with placebo over the double-blind period (P = .0034). The eszopiclone 2-mg group had significantly longer total sleep time (P = .0003) and eszopiclone 1-mg group had significantly shorter sleep latency (P < or = .012) compared with placebo. The eszopiclone 1-mg group was not significantly different from placebo on total sleep time or any other secondary efficacy endpoint. Secondary analysis indicated that the eszopiclone 2-mg group had significantly less wake after sleep onset; significantly fewer and shorter in duration daytime naps; and significantly higher ratings of sleep quality and depth, daytime alertness, and sense of physical well-being compared with placebo (P < .05). Eszopiclone was well tolerated. The most frequent treatment-related adverse event was unpleasant taste. **CONCLUSION:** Nightly treatment with eszopiclone 1 mg effectively induced sleep, while the 2-mg dose was effective in inducing and maintaining sleep. Eszopiclone was well tolerated in elderly patients with primary insomnia and the sleep efficacy was accompanied by significantly less napping and significantly higher ratings of daytime alertness, sense of physical well-being and several quality-of-life parameters at the higher dose.

## Efficacy and safety of eszopiclone across 6-weeks of treatment for primary insomnia

**OBJECTIVE:** Eszopiclone is a new, single-isomer, non-benzodiazepine, cyclopyrrolone agent under investigation for the treatment of insomnia. The present study was a randomized, double-blind, multicenter, placebo-controlled trial conducted to assess the efficacy and safety of eszopiclone in adults with chronic primary insomnia. **RESEARCH DESIGN AND METHODS:** Patients (n = 308) were randomized to receive placebo or eszopiclone (2 mg or 3 mg) for 44 consecutive nights, followed by 2 nights of single-blind placebo. Efficacy was evaluated with polysomnography (Nights 1, 15 and 29) and patient-reports (Nights 1, 15, 29 and 43/44). Next-day residual effects were evaluated using the Digit-Symbol Substitution Test (DSST). **RESULTS:** Eszopiclone 3 mg had significantly less time to sleep onset ($p < or = 0.0001$), more total sleep time and sleep efficiency ($p < or = 0.0001$), better sleep maintenance ($p < or = 0.01$), and enhanced quality and depth of sleep ($p < 0.05$) across the double-blind period compared with placebo. Eszopiclone 2 mg had significantly less time to sleep onset ($p < or = 0.001$), more total sleep time ($p < or = 0.01$) and sleep efficiency ($p < or = 0.001$), and enhanced quality and depth of sleep ($p < 0.05$) compared with placebo, but did not significantly improve sleep maintenance. There was no evidence of tolerance or rebound insomnia after therapy discontinuation. Median DSST scores showed no decrement in psychomotor performance relative to baseline and did not differ from placebo in either eszopiclone group. Treatment was well tolerated; the most common adverse event related to eszopiclone was unpleasant taste. **CONCLUSIONS:** Patients treated with nightly eszopiclone 3 mg had better polysomnographic (through Night 29) and patient-reported measures (through Night 44) of sleep over the 6-week trial. There was no evidence of tolerance or rebound insomnia and no detrimental effects on next-day psychomotor performance using the DSST.

## Sustained efficacy of eszopiclone over 6 months of nightly treatment: results of a randomized, double-blind, placebo-controlled study in adults with chronic insomnia

**STUDY OBJECTIVES:** To determine the long-term efficacy of eszopiclone in patients with chronic insomnia. **DESIGN:** Randomized, double-blind, multicenter, placebo-controlled. **SETTING:** Out-patient, with monthly visits. **PATIENTS:** Aged 21 to 69 years meeting DSM IV criteria for primary insomnia and reporting less than 6.5 hours of sleep per night, and/or a sleep latency of more than 30 minutes each night for at least 1 month before screening. **INTERVENTIONS:** Eszopiclone 3 mg (n = 593) or placebo (n = 195), nightly for 6 months **MEASUREMENTS AND RESULTS:** Efficacy was evaluated weekly using an interactive voice-response system. Endpoints included sleep latency; total sleep time; number of awakenings; wake time after sleep onset; quality of sleep; and next-day ratings of ability to function, daytime alertness, and sense of physical well-being. At the first week and each month for the study duration, eszopiclone produced significant and sustained improvements in sleep latency, wake time after sleep onset, number of awakenings, number of nights awakened per week, total sleep time, and quality of sleep compared with placebo ($P <$ or $= 0.003$). Monthly ratings of next-day function, alertness, and sense of physical well-being were also significantly better with the use of eszopiclone than with placebo ($P <$ or $= 0.002$). There was no evidence of tolerance, and the most common adverse events were unpleasant taste and headache. **CONCLUSIONS:** Throughout 6 months, eszopiclone improved all of the components of insomnia as defined by DSM-IV, including patient ratings of daytime function. This placebo-controlled study of eszopiclone provides compelling evidence that long-term pharmacologic treatment of insomnia is efficacious.

## An evaluation of the efficacy and safety of eszopiclone over 12 months in patients with chronic primary insomnia

**BACKGROUND AND PURPOSE:** A double-blind placebo-controlled study of eszopiclone found significant, sustained improvement in sleep and daytime function. The 6-month open-label extension phase is described herein. **PATIENTS AND METHODS:** Adults (21-64) with primary insomnia who reported sleep duration <6.5 h/night or sleep latency >30 min/night were included. Patient-reported endpoints included sleep and daytime function. Safety and compliance were assessed at monthly clinic visits. The final double-blind month was used as the baseline for efficacy analysis of the open-label period. **RESULTS:** Patients who were initially randomized to double-blind placebo and then switched to open-label eszopiclone (n=111) significantly reported the following: (1) decreased sleep latency, wake time after sleep onset, and number of awakenings; (2) increased total sleep time and sleep quality; and (3) improved ratings of daytime ability to function, alertness and sense of physical well-being compared to baseline (P<or=0.0001 all monthly endpoints). There was no evidence of tolerance on any measure in either group. These subjects (n=360) sustained the double-blind treatment gains for all sleep and daytime parameters, with further significant improvement in a number of measures. Eszopiclone was well tolerated in both groups; unpleasant taste was the only undesirable effect reported by >5% of patients. **CONCLUSIONS:** The significant improvements in sleep and daytime function were evident in those switched from double-blind placebo to 6 months of open-label eszopiclone therapy and were sustained during the 6 months of open-label treatment for those receiving prior double-blind eszopiclone. During 12 months of nightly treatment, eszopiclone 3mg was well tolerated; tolerance was not observed.

## An assessment of the efficacy and safety of eszopiclone in the treatment of transient insomnia in healthy adults

**BACKGROUND AND PURPOSE:** This randomized, double-blind, placebo-controlled study assessed the efficacy and safety of eszopiclone, a non-benzodiazepine hypnotic agent, in healthy adults using the first-night effect model of transient insomnia. **PATIENTS AND METHODS:** A total of 436 healthy, normal sleeping participants were randomized to receive either eszopiclone 1, 2, 3, or 3.5mg, or placebo. Efficacy and next-morning effects were evaluated via polysomnography (PSG), Digit Symbol Substitution Test (DSST), and self-report. **RESULTS:** Patients treated with eszopiclone had significantly less PSG latency to persistent sleep (all doses except 1mg; P< or =0.0001), wake time after sleep onset (all doses; P< or =0.05) and number of awakenings (3 and 3.5mg doses; P<0.005), and greater sleep efficiency (all doses; P< or =0.02) compared with placebo. Self-reported efficacy results were similar to PSG. Self-reported morning sleepiness scores were significantly better for eszopiclone 3 and 3.5mg compared with placebo (P<0.05). Treatment was well tolerated by patients, and the most common treatment-related adverse event was unpleasant taste. **CONCLUSIONS:** In this model of transient insomnia, all doses of eszopiclone were more effective than placebo and were well tolerated by patients.

## Eszopiclone for insomnia

**OBJECTIVE:** To review the pharmacology, pharmacokinetics, efficacy data, and adverse effects of eszopiclone in the treatment of transient and chronic insomnia in adult and geriatric patients. **DATA SOURCES:** A MEDLINE literature search (1966-May 2005) was conducted to retrieve articles and abstracts involving eszopiclone. The manufacturer of the drug provided a general summary of clinical data and abstracts of unpublished Phase III clinical trials. **STUDY SELECTION AND DATA EXTRACTION:** All articles identified from the data sources were reviewed, and information deemed relevant was included for this review. **DATA SYNTHESIS:** Food and Drug Administration approval of eszopiclone was based on 6 double-blind, placebo-controlled trials. Five trials published in abstract or study form were reviewed. The sixth trial was not available for evaluation. An open-label continuation trial was also reviewed. All studies showed statistically significant improvements in sleep parameters in adult and elderly patients treated for insomnia with eszopiclone. **CONCLUSIONS:** The results of the 5 available double-blind, placebo-controlled studies (and 1 open-label, 6-month extension) showed that eszopiclone was safe and effective in the treatment of transient and chronic insomnia in adult and geriatric patients. Tolerance with long-term exposure (6 mo) and rebound insomnia were not observed. The results of the 6-month, open-label extension trial demonstrated that improvements in sleep parameters were sustained.

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