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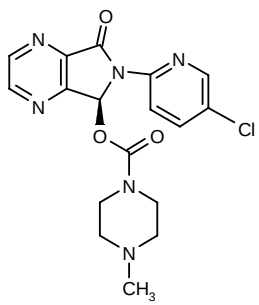
Eszopiclone

Prop INN; USAN

Treatment of Insomnia
GABAergic Transmission Enhancer

(+)-Zopiclone
(*S*)-Zopiclone
Estorra™

(+)-6-(5-Chloro-2-pyridyl)-7(*S*)-(4-methylpiperazin-1-ylcarbonyloxy)-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyrazin-5-one
(+)-4-Methylpiperazine-1-carboxylic acid 6-(5-chloro-2-pyridyl)-7-oxo-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyrazin-5(*S*)-yl ester



$C_{17}H_{17}ClN_6O_3$

Mol wt: 388.8133

CAS: 138729-47-2

EN: 283666

Abstract

Eszopiclone, the (*S*)-enantiomer of the chiral hypnotic drug zopiclone, is currently being reviewed by the FDA as a potential new treatment for insomnia. Results of recent well-designed clinical trials show nightly eszopiclone produces significant improvements in sleep latency, sleep duration and sleep quality in patients with chronic insomnia, without the risk of next-day impairment, tolerance or rebound effects. Eszopiclone showed sustained efficacy and good tolerability in subjects receiving treatment for up to 1 year, and it is currently the only nonbenzodiazepine drug to have completed a long-term, 6-month, placebo-controlled trial.

Synthesis

The esterification of (±)-6-(5-chloro-3-pyridyl)-5-hydroxy-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyrazin-7-one (I), an intermediate in the synthesis of zopiclone (1), with vinyl chloroformate (II) in pyridine gives the racemic carbonate (III), which is submitted to enantioselective hydrolysis or transcarbonatation (with benzyl alcohol, methanol, ethanol, octanol, isopropanol or isobutanol) both catalyzed by *Candida antarctica* (SP 435L) lipase in dioxane, to yield a mixture of racemic (I) – which can be recycled – and the enantiomerically pure (95% e.e.) (*S*)-enantiomer (IV) (2, 3).

Alternatively, racemic (I) can also be esterified with chloromethyl chloroformate (V) in pyridine to provide the corresponding racemic carbonate (VI), which is resolved via *Candida antarctica* lypase B (Chirazyme-L2) catalyzed hydrolysis in toluene to give a mixture of racemic (I) and the (*S*)-enantiomer (96% e.e.) (VII) (4).

The enzymatic hydrolysis of both racemates (III) and (VI) can also be performed with octadecyl-Sepabead inmobilized *Candida antarctica* lypase B in sodium phosphate buffer/dioxane (5).

Finally, both compounds (*S*)-(IV) and (*S*)-(VII) are condensed with 1-methylpiperazine (VIII) in acetone (2-4). Scheme 1.

Eszopiclone can also be obtained by optical resolution of zopiclone by several different methods: i) crystallization of the D-(+)-*O*,*O*'-dibenzoyltartaric acid salt in acetonitrile, followed by treatment with NaOH in dichloromethane/water (6); ii) crystallization of the (+)-malic acid salt in MeOH/acetone followed by treatment with $KHCO_3$ in MeOH water and extraction with dichloromethane/ethyl acetate (7); iii) chiral chromatography over a Chiralpak AS column (8); iv) capillary electrophoresis in the presence of octakis-(2,3,6-tri-*O*-methyl)-γ-cyclodextrin (9).

Introduction

Insomnia, the inability to initiate and/or maintain sleep, is estimated to affect about one-third of the

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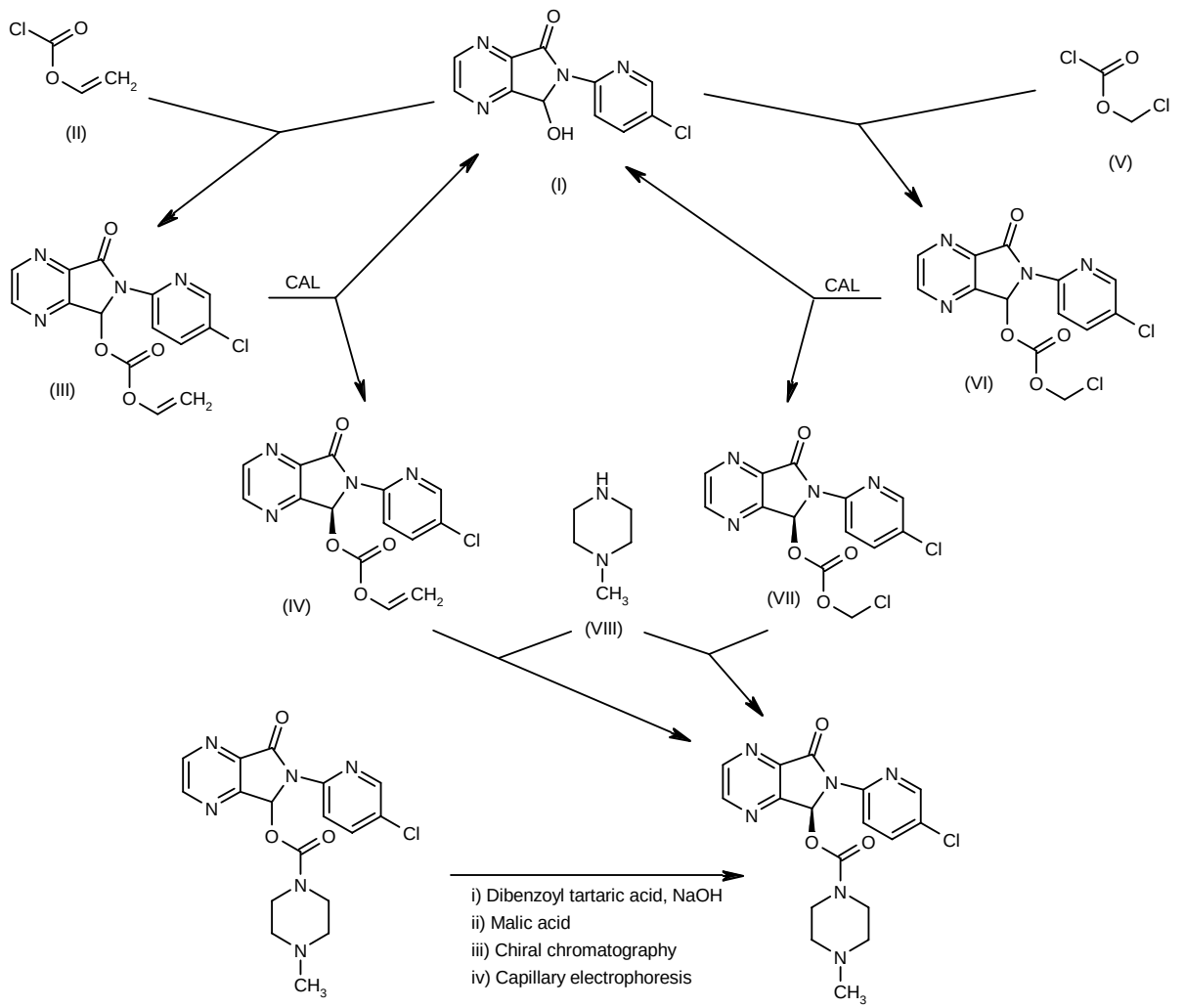
Scheme 1: Synthesis of Eszopiclone



general population in developed countries. Although symptoms are usually short-lived, epidemiological studies indicate that 9-15% of people worldwide experience chronic insomnia, resulting in serious daytime consequences. The prevalence of insomnia is higher in women, the elderly and patients with chronic medical or psychiatric conditions. According to the National Sleep Foundation Sleep in America 2003 poll, about 67% of adults aged 55 years and older reported frequent sleep problems and about 50% experienced symptoms of insomnia at least a few times a week (10-13).

Insomnia is a heterogenous disorder that is associated with a number of different causative factors. Transient or short-term insomnia is usually caused by an acute stressor (*e.g.*, bereavement, loss of a job, illness) or the disruption of circadian patterns (*e.g.*, jet lag, shift work). Chronic insomnia, present for more than 1 month, is typically associated with one or more factors such as an underlying psychiatric or medical disorder (*e.g.*, major depressive disorder, generalized anxiety disorder), chronic drug or alcohol abuse, primary sleep disorders (*e.g.*, restless leg syndrome, sleep apnea), poor sleep hygiene (*e.g.*, environment which is not conducive to sleep) or psychosocial insomnia (*e.g.*, patients who are worried about not sleeping and subsequently engage in self-defeating behaviors) (10, 12, 14, 15).

Persistent lack of sleep can lead to a number of problems during waking hours (*e.g.* fatigue, irritability, anxiety, decreased ability to concentrate and inability to perform complex tasks)(16, 17) and is a strong risk factor for major depression, automobile crashes, industrial accidents, job loss, marital and social problems, poor health, coronary heart disease and metabolic and endocrine dysregulation (10, 18, 19, 20). Insomnia is also associated

with a large economic burden, and the total direct costs of insomnia in the U.S. alone in 1995 were estimated to be about USD 13.9 billion (21).

The main aims in the treatment of insomnia are to address the underlying cause of insomnia, prevent progression from transient to chronic insomnia, and to improve the patient's quality of life. In most cases of transient insomnia, the underlying cause is clear and management typically involves the short-term use of a hypnotic. Treatment of chronic insomnia, however, is more complicated and usually involves a combination of non-pharmacological and pharmacological techniques. Educational and behavioral interventions play a major role in the initial treatment of chronic insomnia; suitable techniques include sleep hygiene education (*e.g.* removal of stimulants such as caffeine, stressful situations); relaxation techniques (*e.g.*, progressive muscle relaxation, guided imagery, hypnosis, meditation, yoga, biofeedback); paradoxical intention (where patients are persuaded to try and stay awake, thereby removing the "performance anxiety" associated with sleeping); stimulus-cognitive therapy (reinforcing associations between the bed/bedroom and falling asleep).Although the majority of patients benefit from such techniques, only about 50% achieve clinically meaningful outcomes and about one-third become good sleepers, so pharmacological intervention is still often utilized (10-12).

Benzodiazepine hypnotics have been the mainstay of pharmacological insomnia treatment since the 1970s and are highly effective in the short-term treatment of insomnia. However, their use is associated with unwanted effects such as potential for dependence, residual effects on waking, rebound insomnia and withdrawal reactions after prolonged use, as well as psychomotor and memory impairment, alterations in sleep architecture and respiratory depression. Nonbenzodiazepine compounds have been developed in an attempt to overcome some of these adverse effects and three other hypnotic drugs are now available: zopiclone, zolpidem and zaleplon (cyclopyrrolone, imidazopydridine and pyrazolopyrimidine agents, respectively). These drugs generally show comparative hypnotic efficacy to benzodiazepines but are better tolerated and are associated with a lower risk for tolerance, abuse, residual day-time symptoms and rebound effects (10, 15, 22).

Antidepressant drugs such as doxepin or amitriptyline (10-50 mg), imipramine (10-75 mg) and trazodone (25-100 mg), can also be effective for the short-term and possibly long-term use in controlling insomnia, particularly in patients with insomnia associated with depression. Other over-the-counter sedative drugs (*e.g.*, antihistamines) and alternative remedies (*e.g.*, kava, valerian) are also commonly used, but their efficacy is not well established (10).

This article reviews the preclinical and clinical profile of a new cyclopyrrolone hypnotic drug, eszopiclone – the (*S*)-enantiomer of zopiclone.

Pharmacological Actions

Eszopiclone is the (*S*)-enantiomer of zopiclone, a hypnotic drug that is commercially available as the racemic mixture. These agents belong to the cyclopyrrolone class of hypnotic drugs and act as agonists at the type A γ-aminobutyric acid (GABA) receptor. Cyclopyrrolones appear to interact with GABA-A in a similar manner to the benzodiazepines. However, differences in receptor function seen after zopiclone and benzodiazepine binding suggest that cyclopyrrolones and benzodiazepines may interact with separate binding domains and/or produce different conformational changes in the GABA-A receptor complex. These differences may account for some of the pharmacodynamic variations observed between these drugs. For example, zopiclone produces comparable anxiiolytic effects to benzodiazepines but is associated with a lower risk of dependence and tolerance in animals and humans (15, 23, 24).

It appears that the (*S*)-enantiomer of zopiclone may be particularly important in mediating the hypnotic effects of zopiclone. Indeed, eszopiclone shows an approximate 50-fold higher binding affinity than its antipode (*R*)-zopiclone at GABA-A receptors, with half-maximal inhibitory concentrations of 21 and 1130 nmol/l, respectively (7).

In rats, zopiclone, eszopiclone, (*R*)-zopiclone and the (*S*)-*N*-desmethylzopiclone metabolite were assessed for their effects on sedation, motor coordination and anxiety. Only zopiclone and eszopiclone (10 mg/kg) showed significant hypnotic effects during a test on locomotor activity. These effects peaked at 30-60 min postdose and were absent during the second hour. At 10 mg/kg, zopiclone and eszopiclone also disrupted motor coordination in the rotarod performance test and showed significant anxiolytic effects in the plus maze test. In contrast, (*R*)-zopiclone failed to produce a significant effect on locomotor activity and showed relatively inconsistent effects on the plus maze test. (*S*)-*N*-Desmethylzopiclone (up to 200 mg/kg) also failed to show an effect on locomotor activity, or on rotarod performance, but had a potent anxiolytic effect on the plus maze test. (*S*)-*N*-Desmethylzopiclone also caused a dose-related effect on the Vogel conflict test and a dose-related reduction of electroconvulsive shock-induced seizure durations, suggesting a potential clinical utility for this metabolite in the treatment of anxiety (25).

The GABA-A-mediated effects of zopiclone, eszopiclone, (*R*)-zopiclone and the (*S*)-*N*-desmethylzopiclone metabolite in monkeys were examined in two drug discrimination assays. In the first assay, the ability of these agents to substitute for the benzodiazepine midazolam was evaluated. Zopiclone (0.32-17.8 mg/kg) and eszopiclone (0.1-10 mg/kg) effectively substituted for midazolam, with both agents showing an 80% or more midazolam-appropriate response. In contrast, (*R*)-zopiclone showed only a 45% midazolam-appropriate response at a dose of 100 mg/kg, suggesting low efficacy for this compound at benzodiazepine receptors. No effect at all was observed for (*S*)-*N*-desmethylzopiclone. A drug with low efficacy at benzodiazepine receptors should antagonize

Table I: Mean ± SD plasma pharmacokinetic parameters of eszopiclone (S)- and (R)-zopiclone (R) following oral administration of zopiclone in healthy volunteers (29, 30).

Dose	C_{max} (ng/ml)		T_{max} (h)		AUC_{∞} (ng·g/ml)		$t_{1/2}$ (h)		CL/F (l/h)	
	S	*R*	*S*	*R*	*S*	*R*	*S*	*R*	*S*	*R*
15 mg	87.3±18.9	44.0±16.1	1.65±1.19	1.48±0.835	691.3±183.3	209.5±62.2	6.65±2.68	3.76±2.98	11.75±3.87	39.59±14.53
7.5 mg	37.54±13.4	23.19±9.15	≈1	≈1	205.26±58.97	79.43±30.18	6.74±4.02	3.15±0.93	14.40±5.47	43.20±15.39

higher efficacy benzodiazepines. To determine whether this is true for zopiclone and its enantiomers, the ability of these agents to substitute for the benzodiazepine antagonist flumazenil in diazepam-treated monkeys was evaluated; none of the drugs showed an effect in this assay (26).

These studies show that eszopiclone, like zopiclone, has benzodiazepine-like effects on preclinical models of sedation, motor coordination and anxiety. Its (*S*)-*N*-desmethyl metabolite has also shown significant anxiolytic effects, without the sedative effects observed with eszopiclone; however, these anxiolytic effects do not appear to be the result of actions at benzodiazepine receptors (25, 26).

Pharmacokinetics

Information regarding the pharmacokinetic profile of eszopiclone is limited at present; however, the pharmacokinetics of racemic zopiclone are well documented. Following oral dosing, zopiclone is rapidly absorbed with a bioavailability of 80% and an elimination half-life of about 5 h. It is extensively metabolized in the liver, probably via cytochrome P450, to 2 major metabolites: the pharmacologically less active *N*-oxide derivative and the nonhypnotic *N*-desmethyl derivative. Approximately 5% of a dose is excreted unchanged in the urine and approximately 30% is found as major metabolites; a further 50% or more is excreted as metabolites via the lungs (23).

The development of techniques to quantify zopiclone enantiomers in plasma have revealed that zopiclone pharmacokinetics are stereoselective (8, 9, 27-31). In healthy volunteers, the maximum plasma concentration (C_{max}) of eszopiclone was approximately 2-fold higher than that of its antipode, (*R*)-zopiclone, following zopiclone administration. The elimination half-life ($t_{1/2}$) was also 2-fold greater for eszopiclone compared with the (*R*)-enantiomer, resulting in a reduced clearance rate for the former. Evaluation of zopiclone enantiomers and its metabolites in urine showed a significantly higher amount of eszopiclone than (*R*)-zopiclone over 48 h, but results for metabolites were highly variable (32, 33) (Table I).

In vitro and *in vivo* binding studies in healthy volunteers also showed that the (*R*)-enantiomer of zopiclone is more strongly bound than eszopiclone to plasma proteins (albumin and α_1-acid-glycoprotein). The total plasma protein binding percentages were 79.3% for zopiclone, 75.1% for eszopiclone and 83.8% for (*R*)-zopiclone; however, these differences were not considered large enough to account for the stereoselective pharmacokinetics of zopiclone (34).

Only one study has evaluated the pharmacokinetics of eszopiclone following administration of eszopiclone. This study included 96 healthy volunteers who were randomized to receive one of three dose levels of zopiclone (2.5-7.5 mg), one of seven dose levels of eszopiclone (1.0-7.5 mg) or placebo. In eszopiclone recipients, dose-related increases in C_{max} and area under the concentration-time curve (AUC) were observed for eszopiclone, with a $t_{1/2}$ of just over 5 h. (*S*)-*N*-Desmethylzopiclone and *N*-oxide-zopiclone also showed a dose-proportional increase in C_{max}, but dose proportionality was not established for AUC due to inaccuracy of extrapolation. An eszopiclone dose of 2.5 mg was found to be equivalent to a zopiclone dose of 5 mg. No significant differences between eszopiclone and zopiclone were observed for any pharmacokinetic parameters at these doses (35) (Table II).

A recent study evaluated the distribution of eszopiclone and (*R*)-zopiclone in the rat. Interestingly, levels of eszopiclone in the brain were higher following administration of (*R*)-zopiclone than following administration of eszopiclone. These results suggest that (*R*)-eszopiclone may be taken up more effectively to the brain where it then undergoes in situ stereoconversion to the (*S*)-enantiomer. The pharmacological significance of these findings is still unclear (36).

Clinical Studies

Eszopiclone has shown significant hypnotic efficacy and good tolerability in two double-blind, randomized, placebo-controlled clinical studies, producing no signs of tolerance, rebound insomnia or next-day residual effects in patients receiving treatment for up to 1 year.

The short-term efficacy of eszopiclone was demonstrated in a study including 308 patients aged 21-64 years with chronic insomnia who were randomized to receive a nightly dose of placebo or eszopiclone 2 or 3 mg for 6 weeks. Efficacy and potential for rebound insomnia were measured using both objective polysomnography measures and subjective patient questionnaires, and next-day residual effects were measured using digit-symbol substitution tests (DSST). Assessments were performed at baseline, after the first dose and at weeks 2, 4 and 6. Compared with placebo, a dose of 2 or 3 mg of eszopi-

Table II: Pharmacokinetic profile of eszopiclone following oral administration of zopiclone and eszopiclone (35).

Dose	C_{max} (ng/ml)	T_{max} (h)	AUC_{∞} (ng·h/ml)	$t_{1/2}$ (h)
Eszopiclone 2.5 mg	25.95	1.53	173.39	5.93
Zopiclone 5 mg	20.10	1.48	156.87	5.41

Table III: Clinical studies of eszopiclone (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Insomnia	Randomized, double-blind, multicenter	Eszopiclone, 2 mg od x 44 d Eszopiclone, 3 mg od x 44 d Placebo	308	Eszopiclone administered once daily at nighttime significantly improved the onset, maintenance, duration, quality and depth of sleep in patients with chronic insomnia. The drug also improved sleep latency, sleep efficiency and total sleep time, and was associated with a beneficial learning effect. No evidence of pharmacological tolerance or next day residual effects was found	37
Insomnia	Randomized, double-blind, multicenter	Eszopiclone, 3 mg od x 6 mo (n=593) Placebo (n=195)	788	Eszopiclone was more effective than placebo in improving sleep maintenance, sleep latency, total sleep time and sleep quality in patients with chronic insomnia. The drug was well tolerated and no pharmacologic tolerance was found	39, 40

clone significantly improved sleep onset (latency to persistent sleep [LPS] and sleep latency), sleep duration, sleep maintenance and the quality and depth of sleep. Eszopiclone 3 mg also produced significant improvement in objective and subjective wake time after sleep onset (WASO) versus placebo. There was no evidence of residual daytime effects, with both the placebo and eszopiclone groups showing a similar improvement in DSST scores over baseline over the course of the trial. In addition, when compared with baseline, there were no rebound effects on sleep onset or sleep maintenance following eszopiclone withdrawal. Eszopiclone was well tolerated, and the most common event reported across all treatment groups was unpleasant taste (37, 38) (Table III).

In a recent multicenter trial, 788 patients aged 21-69 years with chronic insomnia were randomized to receive either placebo or 3 mg of eszopiclone once every night for 6 months. Patients had a diagnosis of DSM-IV insomnia with a history of less than 6.5 hours of sleep per night and a sleep onset of more than 30 min, and were not enriched for WASO problems. The primary efficacy endpoints of subjective sleep maintenance, sleep latency, total sleep time and sleep quality were assessed at weekly intervals using an interactive voice response system, and safety was assessed monthly. The majority of patients completed the 6-month clinical trial: 60.5% in the eszopiclone group and 56.6% in the placebo group. In eszopiclone-treated patients who finished the trial, significant improvements were observed for sleep maintenance (WASO, number of awakenings and number of nights awakened), sleep latency as well as the time and quality of sleep compared to placebo. Furthermore, patients receiving eszopiclone showed no evidence of pharmacologic tolerance or abuse and the most frequent adverse effect was unpleasant taste (26.1% *vs.* 5.6% for eszopiclone and placebo recipients, respectively). Vital signs, laboratory parameters, ECGs and physical and neurological examinations revealed no safety concerns. Patients in this trial were allowed to continue eszopiclone treatment in an open-label continuation study. At the end of 12 months, there was no evidence of a loss of effect or the development of tolerance in patients receiving eszopiclone. Furthermore, eszopiclone recipients showed sustained improvements in daytime alertness and daytime functioning over 12 months (39-41) (Table III).

No studies have compared eszopiclone with other hypnotic drugs. However, the hypnotic efficacy of zopiclone is well documented, and this drug has similar or greater efficacy than a number of benzodiazepines (nitrazepam, flunitrazepam, temazepam, triazolam and midazolam), as well as the nonbenzodiazepine hypnotic zolpidem in well-designed studies. It is unknown whether eszopiclone will show similar results (23, 42).

Eszopiclone is being developed by Sepracor as a potential new treatment for insomnia. Sepracor submitted a New Drug Application for eszopiclone to the FDA on January 31, 2003, which was accepted for filing on April 1, 2003 and is currently undergoing FDA review (43, 44).

Conclusions

Eszopiclone is the (*S*)-enantiomer of zopiclone, a cyclopyrrolone hypnotic drug that is commercially available as the racemate. Eszopiclone is thought to be mainly responsible for the beneficial effects of zopiclone, and it shows a 50-fold greater affinity to GABA-A receptors than the (*R*)-enantiomer. It is rapidly absorbed following oral administration and has a half-life of just over 5 h. This pharmacokinetic profile supports rapid sleep-inducing effects and sustained effects throughout the night without the risk of residual next-day effects. Although evidence is still limited at this stage, eszopiclone treatment appears to provide effective relief from a range of insomnia symptoms, including problems of falling asleep, maintaining sleep, as well as complaints of poor sleep quality and impaired day-time function. The positive effects of eszopiclone are sustained with long-term treatment for up to 12 months, with treated subjects showing no evidence of loss of effect or the development of tolerance. In addition, eszopiclone has a good tolerability profile, with an unpleasant taste being the only reported adverse event from clinical trials thus far. These characteristics make eszopiclone a promising candidate for the short-term treatment of insomnia as well as maintenance therapy for chronic sufferers. In fact, eszopiclone is currently the only nonbenzodiazepine drug to have completed a 6-month, placebo-controlled trial. However, the efficacy and tolerability of eszopiclone in relation to other hypnotics has not yet been investigated so the positioning of this compound in terms of the overall management of the disease is still unclear.

Source

Sepracor Inc. (US); licensed from Aventis Pharma AG (CH).

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