

# Eszopiclone

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## Introduction

Eszopiclone, marketed by Sepracor under the brand-name Lunesta, is a nonbenzodiazepine hypnotic agent that is a pyrrolopyrazine derivative of the cyclopyrrolone class, used as a treatment for insomnia.

IUPU name : (+)-(5S)-6-(5-chloropyridin-2-yl)-7-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-yl 4-methylpiperazine-1- carboxylate.

molecular weight : 388.81

half life 6 hours

empirical formula : C<sub>17</sub>H<sub>17</sub>ClN<sub>6</sub>O<sub>3</sub>

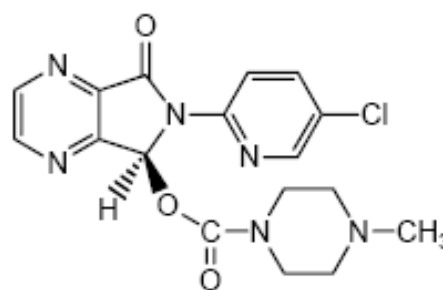
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Eszopiclone is a white to light-yellow crystalline solid. Eszopiclone is very slightly soluble in water, slightly soluble in ethanol, and soluble in phosphate buffer (pH 3.2).

## Lead compound discovery

### Nonbenzodiazepine

The nonbenzodiazepines, also called benzodiazepine-like drugs, are a class of psychoactive drugs whose pharmacological actions are similar to those of the benzodiazepines, but are structurally distant or unrelated to the benzodiazepines on a chemical level. They have similar side effects and benefits and risks as the benzodiazepines.

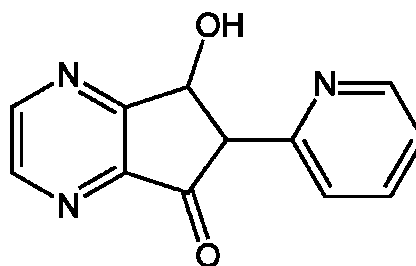
There are currently three major chemical classes of nonbenzodiazepines:

Imidazopyridines, Pyrazolopyrimidines, Cyclopyrrolones

## Cyclopyrrolones

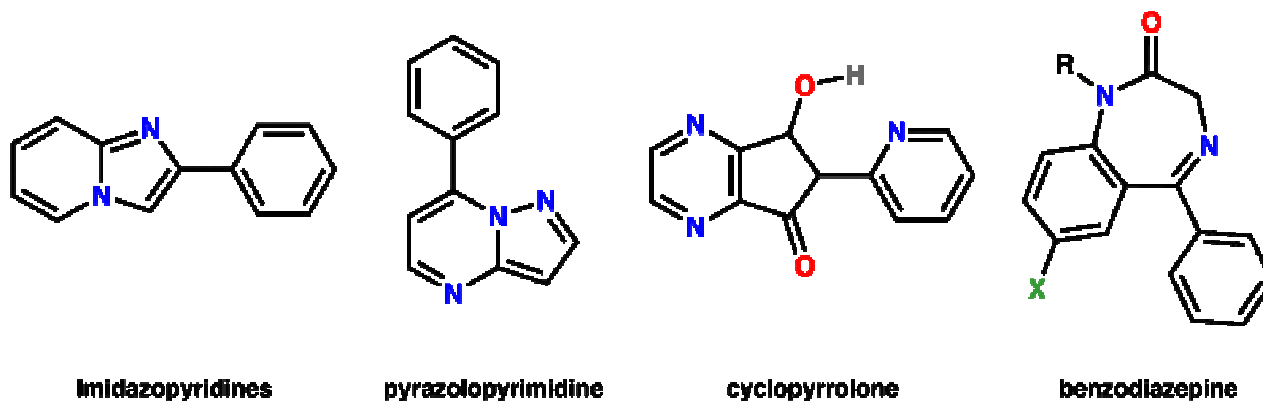
Cyclopyrrolones are a family of hypnotic and anxiolytic nonbenzodiazepine drugs with similar pharmacological profiles to the benzodiazepine derivatives.

Eszopiclone belongs to cyclopyrrolones.



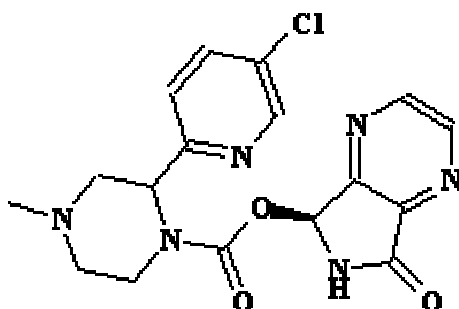
## Molecular Modification

Nonbenzodiazepine is benzodiazepine-liked drug. It contains four main groups, including Imidazopyridines, Pyrazolopyrimidine, Cyclopyrrolone and Benzodiazepine. Their structures are shown below:



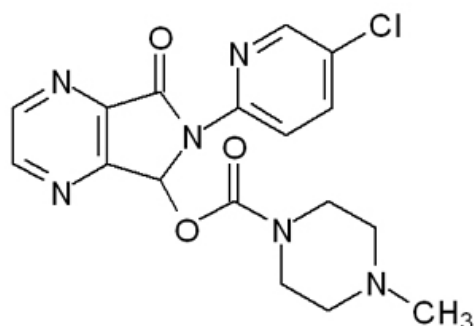
Eszopiclone is under the class of Cyclopyrrolone. It has the structure like this:

## **Eszopiclone**



and the systematic name is (S)-6-(5-Chloro-2-pyridinyl)- 7-oxo- 6,7-dihydro- 5H-pyrrolo[3,4-b]pyrazin-5-yl- 4-methyl- 1-piperazinecarboxylate.

Molecular formulation of Eszopiclone is modified from Zopiclone, which is also a member of the class, Cyclopyrrolone. It has the structure like this:



and it has the IUPAC name as (RS)-[8-(5-chloropyridin-2-yl)- 7-oxo-2,5,8-triazabicyclo [4.3.0]nona-1,3,5-trien-9-yl] 4-methylpiperazine-1-carboxylate

Eszopiclone is the S-enantiomer of zopiclone, and is more active and less toxic than the racemic zopiclone.

The invention relates of eszopiclone to a reproducible process for the preparation of s zopiclone and it's intermediate 6-(5-chloropyridyl-2-yl )-5-hydroxy-7-oxo-5,6 dihydropyrrolo [3,4-b] pyrazine. The said invention further relates to effective method for resolution of zopiclone into its enantiomers and furthermore provides a method of recycling of (R)-zopiclone.

Eszopiclone's mechanism of action is via the benzodiazepine receptor-GABA complex. The optical purity of the eszopiclone is preferably more than about 99.9%.

## **Formulation development**

### **Recommended Dosages:**

For treatment to improve sleep onset and/or sleep maintenance :

2 mg–3 mg for adult patients (aged 18–64 years)

2 mg for older adult patients aged 65 years or older

1 mg dose for older adult patients whose problems are related to sleep onset.

Care should be taken in choosing an appropriate hypnotic drug.

It should be initiated at the lowest possible dose to minimise side effects.

Eszopiclone possesses potent activity in treating sleep disorders such as insomnia

while avoiding the usual adverse effects including but not limited to drowsiness, next day effects tiredness in the morning, inability to concentrate and headache. Eszopiclone is also used to treat convulsive disorders such as epilepsy in one of the formulation in tablet form.

The term “pharmaceutically acceptable salt” refers to salts prepared from pharmaceutically acceptable non-toxic acids or bases, including inorganic acids and bases and organic acids and bases. Suitable pharmaceutically acceptable acids are used for forming salts with eszopiclone, without limitation. In one embodiment, eszopiclone is formulated as a succinate salt. In another embodiment, eszopiclone is formulated as a fumarate salt.

However, any such optional ingredient must be compatible with combination of active ingredients to insure the stability of the formulation. In some embodiment comprising eszopiclone or its salts, wherein the percentage of active ingredient in the total compositions is in the range of from about 1% to about 10% w/w.

Eszopiclone and O-desmethylvenlafaxine (The term "O-desmethylvenlafaxine" as used herein encompasses both racemic (.+-.)-O-desmethylvenlafaxine, and individual enantiomers (-)-O-desmethylvenlafaxine and (+)-O-desmethylvenlafaxine.) are chiral compounds that can exist as a racemic mixture, a non-equal mixture of enantiomers, or as a single enantiomer. Importantly, the recitation of a compound that can exist as a racemic mixture, a non-equal mixture of enantiomers of different ratios, or a single enantiomer is meant to encompass all three aforementioned forms, unless stated otherwise.

For example, compositions comprising eszopiclone contain the S-enantiomer of zopiclone in at least 90% e.e. More preferably, compositions comprising eszopiclone contain the S-enantiomer of zopiclone in at least 95% e.e. (The value of e.e. will be a number from 0 to 100, zero being racemic and 100 being pure, single enantiomer.) Even more preferably, such compositions comprising eszopiclone contain the S-enantiomer of zopiclone in at least 98% e.e. Most preferably, such compositions comprising eszopiclone contain the S-enantiomer of zopiclone in at least 99% e.e.

### **Safety tests and human trial**

All clinical trials of eszopiclone published so far are industry funded by the pharmaceutical manufacturer of eszopiclone, Sepracor.

Eszopiclone was studied for up to 6 months in a group of patients which showed no signs of tolerance or dependence in a study funded and carried out by Sepracor.

The studies used both objective and subjective assessments to evaluate the efficacy of eszopiclone.

The objective assessments included:

- polysomnography (PSG)
- latency to persistent sleep (LPS) defined as the time from lights out to the first 10 minutes of sleep
- wake time after persistent sleep onset (WASO)
- total sleep time (TST)
- number of awakenings (NAW).

Subjective assessments often were also LPS, WASO, NAW, and TST but as assessed by the patient; Sleep quality and quality of life were also reported by the patient.

Study	Intervention	LPS (min)	SE (%)	WASO (min)	TST (min)	NAW
Zammit <sup>13</sup> Mean age: 39.8 yr Caucasian: 88.2% Female: 64.6%	ESZ 2 mg (n=104)	15*	88.1*	37.1		8.5
	ESZ 3 mg (n=105)	13.1*	90.1*	33.8*		5.7
	PL (n=99) 44 nights continuously	29	85.7	44.1		8
Kryslak <sup>4</sup> Mean age: 44 yr Caucasian: 79% Female: 83%	ESZ 3 mg (n=695)	30**		21	302.6**	1.6**
	PL (n=198) 6 months	45		30 (p=0.0032)	345	2

LPS=latency to persistent sleep, SE= sleep efficiency, WASO=wake time after sleep onset, TST=total sleep time, NAW=number of awakenings/night, ESZ=eszopiclone, PL=placebo; \*p<0.0001, \*\*p<0.0001 vs PL; †p<0.01 vs PL; ‡sleep efficiency (ratio of TST to total time in bed of 8 hrs x 100)

Three studies with eszopiclone have been published.

### **First two studies**

#### Background

The first two studies were randomized, double-blind, placebo controlled in patients who met the DSM-IV criteria for primary insomnia. The inclusion criteria were similar in that patients had to have total sleep time of less than approximately 6.5 hours per night and needed more than 30 minutes to fall asleep. The baseline BMI and the number of females were significantly higher (p<0.05) in the treatment groups compared to placebo; however, these variables did not change the conclusions of the study when incorporated as covariates in the efficacy analysis model.

#### Objective assessment

In the study by Zammit et al, eszopiclone increased slightly but significantly the time in stage two of sleep (219 min, 244 min, 252 min for placebo, 2 mg, 3 mg, respectively; p<0.05 for both doses of eszopiclone vs placebo) but the amount of time in the other

stages of sleep was not significantly affected.

#### Subjective assessments

The endpoints assessed in the six-month study with eszopiclone were patient assessments.

The primary endpoint was the average sleep latency over the last three months of the first six months of the study.

The secondary endpoint was total sleep time over the same time period.

These data were not presented or discussed. The authors stated that seven other time points (week one, and monthly values for the six months) and nine different endpoints were analyzed because they were more informative. Data reported in the following table for this study are data from month six.

\*The effectiveness and safety of long-term use of these agents remain to be determined.

\*Safety and efficacy in children less than 18 years has not been established.

### **The third studies**

#### Background

The third published study evaluated the safety and efficacy of eszopiclone in transient insomnia using a “first-night effect” model. The study was a prospective, multi-center, randomized, double-blind, placebo-controlled, parallel-group sleep laboratory study. Study participants were normal, healthy adults with normal sleep habits, defined as bedtime between 21:00 and 24:00, sleep onset in less than 30 minutes, sleep lasting from 6.5-10 hours and no report of daytime functioning problems due to sleep. The primary endpoint was objective LPS. Other assessments include PSG measured WASO, sleep efficiency, NAW, sleep architecture, as well as patient reported LPS, TST, NAW, WASO, quality of sleep, and depth of sleep. Study medication was administered at doses of 1, 2, 3 and 3.5 mg.

#### Objective assessments

Latency to persistent sleep was significantly shorter with eszopiclone compared to placebo for all doses ( $p < 0.0001$ ) except 1 mg ( $p = 0.06$ ). Wake time after sleep onset was also significantly less with eszopiclone compared with placebo ( $p \leq 0.05$ ). The reduction in NAW was significant with eszopiclone 3 mg and 3.5 mg but not with 1 and 2 mg. Sleep efficiency was also improved with eszopiclone ( $p \leq 0.02$ ).

#### Subjective assessments

The subjective assessments were similar to the objective measures in most of the

assessments; the few exceptions were that in some cases when there was a difference by dose in the objective measures, there was not a difference in the subjective measures and vice versa. There were no significant differences in time spent in the various sleep stages between placebo and all doses of eszopiclone except 3.5 mg. The results of a double-blind, placebo controlled study with eszopiclone in 264 patients age 65-85 years with primary insomnia are available in abstract only. Fourteen nights of eszopiclone 2 mg was compared with placebo.

### **Approval for marketing**

Sepracor Submits LUNIVIA(R) (LUNESTA(R) in U.S.) Marketing Authorization Application (MAA) for Europe in 2007

Lupin Pharmaceuticals, Inc. (LPI) received Marketing Authorization Application (MAA) in Europe for Eszopiclone tablets, 1 mg, 2 mg and 3 mg from European Medicines Agency (EMA) in October 24, 2008

Eszopiclone tablets in the strength of 1 mg, 2 mg and 3 mg received a tentative approval for the company's abbreviated new drug application (ANDA) from the US Food and Drug Administration (USFDA) in March 23, 2010

\* not marketing approval , till now in US, Eszopiclone is a schedule IV controlled substance under the Controlled Substances Act