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Newcastle University

Health Technology Briefing
March 2024

Eszopiclone for treating insomnia

Company/Developer	Leith Healthcare/axunio pharma GmbH

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 37991	NICE ID: Not available	UKPS ID: 672961

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Eszopiclone has been developed for the treatment of insomnia in adults. Insomnia is difficulty getting to sleep or staying asleep for long enough to feel refreshed the next morning. It is a common problem thought to regularly affect around one in every three people in the UK and is particularly common in elderly people. Insomnia is comorbid with several conditions, such as rheumatoid arthritis, depression and menopause. Insomnia has a negative impact on a wide range of daytime functions, including social, emotional, and physical domains, and chronic insomnia affects cognitive and physical functioning.

Eszopiclone is in a class of medications called hypnotics, which work by slowing activity in the brain to allow sleep. Eszopiclone is given orally, and it has a relatively short half-life and rapid onset of action. Indications for eszopiclone in the treatment of insomnia are not limited to its short-term use, as its efficacy and safety have also been demonstrated in dosing studies of six - to-twelve-month duration.

Proposed Indication

For the treatment of insomnia in adults.[1]

Technology

Description

Eszopiclone (Lunivia)[a] is a non-benzodiazepine (also known as hypnotics), benzodiazepine (BZ) receptor agonist of the cyclopyrrolone class that causes neural inhibition and helps to induce sleep.[2] Indications for eszopiclone in the treatment of insomnia are not limited to its short-term use, as its efficacy and safety have also been demonstrated in dosing studies of six to twelve month duration.[3] Eszopiclone is thought to enhance the effects of gamma-aminobutyric acid (GABA) at the GABA-A receptor.[4] There are a number of subtypes of this receptor which are relevant for sleep not only because of their different location in the brain, but also because some insomnia drugs are selective for a particular subtype.[4] Eszopiclone is particularly efficacious at alpha 2 receptors, which acts as a sleep/wake switch, and alpha 3 receptors, which plays a role in regulating sleep and mood.[5]

Eszopiclone has been in several clinical developments for the treatment of insomnia related to various conditions including rheumatoid arthritis, perimenopause or menopause, major depressive disorder and chronic insomnia in elderly people.[6-9] In the phase III clinical trial (Eszo, NCT01100164), patients with symptomatic insomnia were randomised to receive eszopiclone 3 mg or zopiclone 7.5 mg, both orally, for four weeks.[3]

Key Innovation

Eszopiclone is a non-benzodiazepine hypnotic that is a pyrrolopyrazine derivative of the cyclopyrrolone class with a chemical structure unrelated to pyrazolopyrimidines, imidazopyridines, benzodiazepines, barbiturates, or other medications with known hypnotic properties.[10] Eszopiclone has selectivity for certain BZ receptor subtypes and has a relatively short half-life and rapid onset of action.[2] Eszopiclone is rapidly absorbed following oral administration.[11] Its peak plasma concentrations are achieved about an hour after oral administration.[10] Eszopiclone fast induces sleep and decreases sleep latency. It also aids in the maintenance of sleep, preventing frequent awakenings.[12]
Eszopiclone will provide an additional treatment option for insomnia in adults.

Regulatory & Development Status

Since 2004, eszopiclone has been marketed in the US for the treatment of insomnia.[13]

Eszopiclone is also in phase II/III clinical development, in the US, for obstructive sleep apnoea.[14]

Patient Group

Disease Area and Clinical Need

Insomnia is difficulty getting to sleep or staying asleep for long enough to feel refreshed the next morning. It is a common problem thought to regularly affect around one in every three people in the UK and is particularly common in elderly people.[15,16] Although the health consequences can be severe, few patients with this disorder are diagnosed and treated appropriately. In addition to negative impacts on a wide range of daytime functions, affecting social, emotional, and physical domains, chronic insomnia affects cognitive

[a] Information provided by Leith Healthcare

and physical functioning. Indeed, compared with people who do not suffer from insomnia, those who present this affliction are more prone to accidents and have higher rates of work absence, decreased work performance, decreased quality of life and increased use of health care resources.[3] Insomnia can be triggered by a number of possible factors including worry and stress, underlying health conditions, and alcohol or drug use.[15] Prevalence of insomnia is higher in people with comorbid conditions such as chronic obstructive pulmonary disease, heart failure, chronic pain and psychiatric conditions; with around half of all people diagnosed with insomnia having a comorbid psychiatric disorder.[16]

In England (2022-2023), there were 208 finished consultation episodes (FCE) for patients with a primary diagnosis of nonorganic sleep disorders (ICD-10 code F51, which includes primary insomnia), resulting in 10 day cases and 353 FCE bed days.[17]

Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) recommends the following pharmacological treatment options for insomnia:[18-20]

- Z drugs (hypnotics) as a short-term treatment (up to two weeks) e.g., zolpidem, zopiclone
- Modified-release melatonin for people over 55 years of age with persistent insomnia for up to 13 weeks
- Daridorexant for treating insomnia in adults with symptoms lasting for 3 nights or more per week for at least 3 months, and whose daytime functioning is considerably affected, only if cognitive behavioural therapy for insomnia (CBTi) has been tried but not worked, or CBTi is not available or is unsuitable.

Clinical Trial Information

Trial	**Eszo;** NCT01100164; A Phase III, Non-inferiority, Double-blind, Unicenter Clinical Trial With Two Treatment Arms - Test Group With Eszopiclone 3 mg Versus Zopiclone 7.5 mg - for the Treatment of Insomnia **Phase III** - Completed **Location(s):** Brazil **Study completion date:** April 2012
Trial Design	Randomised, parallel assignment, double masked
Population	N=263 (actual); adults aged between 20 to 64 years old with symptomatic primary insomnia for at least 3 months
Intervention(s)	Eszopiclone 3mg tablet, once a day (30 minutes before lying down to sleep for a period of 4 weeks of treatment)
Comparator(s)	Zopiclone 7.5mg tablet, once a day (30 minutes before lying down to sleep for a period of 4 weeks of treatment)
Outcome(s)	**Primary outcome measure:** Determine whether eszopiclone is non-inferior to the reference drug zopiclone in the treatment of insomnia. The latency to persistent sleep will be used as a primary endpoint at the end of the treatment, measured by polysomnography. See trial record for full list of other outcomes.

Results (efficacy)	The primary efficacy analysis demonstrated the non-inferiority of eszopiclone over zopiclone. Analysis of objective parameters assessed by polysomnography showed that eszopiclone increased total sleep time and also improved sleep efficiency.[3]
Results (safety)	The safety profile of both study treatments was similar and the most common events reported in both groups were dysgeusia, headache, dizziness, irritability and nausea. Adverse events (AE) were observed in 223 patients, 109 (85.2%) in the eszopiclone group and 114 (87.7%) in the zopiclone group.[3]

Trial	NCT00386334; A Long-Term Safety and Efficacy Study of Eszopiclone in Elderly Subjects With Primary Chronic Insomnia **Phase IV** - Completed **Location(s):** United States **Study completion date**: February 2008
Trial Design	Randomised, parallel assignment, triple masked
Population	N=388 (actual); elderly adults aged 65 to 85 years with primary chronic insomnia
Intervention(s)	Eszopiclone 2 mg tablet once per day in the evening
Comparator(s)	Matched placebo
Outcome(s)	**Primary outcome measure:** Mean change from baseline in subject-reported total sleep time (sTST) averaged over the 12-week double blind study period [timeframe: baseline (week 0), day 1 (post first dose)-12 weeks)] See trial record for full list of other outcomes.
Results (efficacy)	Subjects treated with 2 mg eszopiclone slept longer at night on average and at every individual time point compared to baseline than placebo subjects, as measured by TST over the 12-week double-blind period (P < 0.0001). Mean sTST over the double-blind period for eszopiclone-treated subjects was 360.08 min compared to 297.86 min at baseline, a mean change of 63.24 min. Over the double-blind period, eszopiclone-treated subjects also experienced a significantly greater improvement in subject-reported sleep latency (sSL) compared to placebo, with a mean decrease of 24.62 min versus a mean decrease of 19.92 min, respectively (P = 0.0014). Eszopiclone subjects also experienced a significantly greater decrease in wake time after sleep onset (WASO) (mean decrease of 36.4 min) compared to placebo subjects (decrease of 14.8 min) (P < 0.0001). Post-discontinuation, sleep parameters were statistically improved versus baseline for eszopiclone (P-values < or = 0.01), indicating no rebound.[21]
Results (safety)	The most common AEs (> or = 5%) were headache (eszopiclone 13.9%, placebo 12.4%), unpleasant taste (12.4%, 1.5%), and nasopharyngitis (5.7%, 6.2%).[21]

Trial	NCT00235508; The Efficacy of Eszopiclone 3 mg as Adjunctive Therapy in Subjects With Insomnia Related to Generalized Anxiety Disorder **Phase IV** - Completed **Locations(s):** United States **Study completion date**: April 2006
Trial Design	Randomised, parallel assignment, triple masked
Population	N=420; adults aged 18 to 64 years with insomnia related to generalised anxiety disorder
Intervention(s)	Eszopiclone 3 mg at bedtime
Comparator(s)	Matched placebo
Outcome(s)	**Primary outcome measure:** The change from baseline in subjective sleep latency averaged over the double-blind treatment period in time frame of 8 week. See trial record for full list of other outcomes.
Results (efficacy)	Compared with treatment with placebo and escitalopram, treatment with eszopiclone and escitalopram resulted in significantly improved sleep and daytime functioning (P < .05), with no evidence of tolerance. Patients taking eszopiclone and escitalopram had greater improvements in total Hamilton Anxiety Scale (HAM-A) scores at each week (P < .05) and at weeks 4 through 10 with the insomnia item removed. Clinical Global Impressions (CGI) of Improvement scores were improved with eszopiclone and escitalopram at every point (P < .02), while CGI of Severity of Illness scores were not significantly different after week 1. The HAM-A response (63% vs 49%, respectively, P = .001) and remission (42% vs 36%, respectively, P = .09) rates at week 8 were higher in patients treated with eszopiclone and escitalopram than those treated with placebo and escitalopram, and median time to onset of anxiolytic response was significantly reduced (P < or = .05). After eszopiclone discontinuation, there was no evidence of rebound insomnia, and while treatment differences in anxiety measures were maintained, differences in sleep outcomes were not.[22]
Results (safety)	Overall AE rates were 77.6% with cotherapy and 67.9% with monotherapy. The most common adverse events with cotherapy were unpleasant taste, headache, dry mouth, and somnolence.[22]

Trial	NCT00367965; The Effect of Eszopiclone 3 mg Compared to Placebo on Daytime Function in Subjects With Insomnia Related to Rheumatoid Arthritis **Phase III** - Completed **Location(s)**: United States **Study completion date:** November 2004
Trial Design	Randomised, parallel assignment, triple masked

Population	N=153 (actual); adults aged 25 to 64 years with insomnia related to rheumatoid arthritis (RA)
Intervention(s)	Eszopiclone 3 mg
Comparator(s)	Matched placebo
Outcome(s)	**Primary outcome measure:** Mean subjective wake time after sleep onset (WASO) in time frame of 1 week See trial record for full list of other outcomes.
Results (efficacy)	Eszopiclone significantly improved all patient-reported sleep measures (WASO, SL, and TST), sleep quality, depth of sleep, and daytime function ($P < .05$ vs placebo). At week 4, 48% of eszopiclone-treated patients had no clinically meaningful insomnia as assessed by ISI score (versus 30% of placebo-treated patients, $P = .03$). Eszopiclone was significantly better than placebo on some RA-associated pain measures: (1) overall ($P = .05$), pain ($P = .006$), and pain and other symptoms ($P = .02$) scores of the Arthritis Self-Efficacy Scale, (2) tender joint counts ($P = .03$) and pain severity scores ($P = .023$), (3) the activities domain of the Health Assessment Questionnaire-Disability Index ($P = .04$), and (4) the role physical ($P = .03$) and bodily pain ($P = .01$) scales of the 36-item Medical Outcomes Study Short-Form General Health Survey.[23]
Results (safety)	The most commonly reported AE with eszopiclone were unpleasant taste and transient increases in RA symptoms.[23]

Trial	NCT00352144; A Six-Month, Chronic Efficacy and Safety Study of Eszopiclone in Adult Subjects With Primary Insomnia: A Randomized Double-Blind, Placebo-Controlled Study **Phase III -** Completed **Location(s):** United States **Study completion date:** October 2004
Trial Design	Randomised, parallel assignment, triple masked
Population	N=830 (actual); adults aged 21 to 63 years with primary insomnia and reports sleeping no more than 6.5 hours per night and/or taking more than 30 minutes each night to fall asleep for at least one month prior to screening
Intervention(s)	Eszopiclone 3 mg tablet
Comparator(s)	Matched placebo
Outcome(s)	**Primary outcome measure:** Average of Subjective sleep latency in days -14, 1, 30, 60, 90, 120, 150, 180 See trial records for full list of other outcomes.
Results (efficacy)	Patient-reported sleep and daytime function were improved more with eszopiclone than with placebo at all months (P <0.001). Eszopiclone reduced

	Insomnia Severity Index scores to below clinically meaningful levels for 50% of patients (vs 19% with placebo; P <0.05) at Month 6. SF-36 domains of Physical Functioning, Vitality, and Social Functioning were improved with eszopiclone vs placebo for the Month 1-6 average (P < 0.05). Similarly, improvements were observed for all domains of the Work Limitations Questionnaire with eszopiclone vs placebo for the Month 1-6 average (P <0.05).[24]
Results (safety)	Overall 6-month AE rates were 75.7% in the eszopiclone group compared with 58.9% in the placebo group (P <0.05). The majority of events were rated mild or moderate in severity.[24]

Trial	**DREAMDD; NCT00368030;** Depression Response to Eszopiclone in Adults With Major Depressive Disorder (DREAMDD): A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, 8-Week, Safety & Efficacy Study of Eszopiclone 3 mg Compared to Placebo in Subjects With Insomnia Related to MDD **Phase III** - Completed **Location(s)**: United States **Study completion date:** October 2004
Trial Design	Randomised, parallel assignment, double masked
Population	N=545 (actual); adults aged 21 to 64 years with insomnia related to major depressive disorder (MDD)
Intervention(s)	Eszopiclone 3mg QD
Comparator(s)	Placebo
Outcome(s)	**Primary outcome measure:** Mean subjective WASO in a time frame of one week See trial record for the full list of other outcomes.
Results (efficacy)	Patients in the eszopiclone + fluoxetine group had significantly decreased sleep latency, wake time after sleep onset (WASO), increased total sleep time (TST), sleep quality, and depth of sleep at all double-blind time points (all p < .05). Eszopiclone co-therapy also resulted in significantly greater changes in Hamilton Depression Scale (HAM-D-17) scores at Week 4 (p = .01) with progressive improvement at Week 8 (p = .002); significantly improved CGI-I and CGI-S scores at all time points beyond Week 1 (p < .05); and significantly more responders (59% vs. 48%; p = .009) and remitters (42% vs. 33%; p = .03) at Week 8.[25]
Results (safety)	Treatment was well tolerated, with similar adverse event and dropout rates[25]

Trial	NCT01710631; A Randomized, Double-Blind, Placebo-Controlled and Open-Label Twelve Month Study of the Safety of (S)-Zopiclone in Adult Subjects With Insomnia **Phase III -** Completed **Location(s):** No location data

	Study completion date: August 2002
Trial Design	Randomised, parallel assignment, quadruple masked
Population	N=791 (actual); adults aged 21 to 64 years with primary insomnia
Intervention(s)	Eszopiclone 3 mg (comprised of either two 1.5 mg tablets, or one 1 mg tablet and one 2 mg tablet).
Comparator(s)	Matched placebo
Outcome(s)	**Primary outcome measure:** Average sleep latency over the last half of the double-blind study period ("last-three-month average" = mean of the monthly averages for months 4, 5, and 6) See trial record for full list of other outcomes.
Results (efficacy)	Decreased sleep latency, wake time after sleep onset, and number of awakenings; increased total sleep time and sleep quality; and 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.[26]
Results (safety)	Eszopiclone was well tolerated in both groups; unpleasant taste was the only undesirable effect reported by >5% of patients.[26]

Estimated Cost

Cost of eszopiclone was confidential at the time of producing this briefing.

Relevant Guidance

NICE Guidance

- NICE technology appraisal guidance. Daridorexant for treating long-term insomnia (TA922). October 2023.
- NICE technology appraisal guidance. Guidance on the use of zaleplon, zolpidem and zopiclone for the short-term management of insomnia (TA77). April 2004.
- NICE medical technology guidance. Sleepio to treat insomnia and insomnia symptoms (MTG70). May 2022.

NHS England (Policy/Commissioning) Guidance

- NHS Devon Partnership. Prescribing Guideline; Pharmacological Treatment of Insomnia (PG02) May 2021.
- NHS Southern Health. Guidelines for Treatment of Primary Insomnia (SH CP 136) October 2019.

Other Guidance

- European insomnia guideline. European guideline for the diagnosis and treatment of insomnia. September 2017.[27]
- European Medicines Agency. Guideline on medicinal products for the treatment of insomnia. February 2011.[28]

Additional Information

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NB: This briefing presents independent research funded by the National Institute for Health and Care Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.