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## Piromelatine: A novel melatonin-serotonin agonist for the treatment of insomnia disorder and neurocognitive comorbidities

Nava Zisapel<sup>1</sup> and Moshe Laudon<sup>2</sup>

<sup>1</sup>Tel Aviv University, Israel

<sup>2</sup>Neurim Pharmaceuticals Ltd., Israel

Insomnia affects 30%-50% of the general population and even more so (63%) among patients with mild cognitive impairments (MCI). Alzheimer's disease (AD) risk among insomnia patients is approximately 3 fold that of good sleepers. Furthermore, poor sleep quality is associated with faster cognitive decline and may be an early marker of cognitive decline in mid life. Improvement of sleep may be critically important for maintaining or enhancing cognitive function in patients with MCI or AD. Current hypnotic medications (benzodiazepines and benzodiazepines-like) are associated with cognitive and memory impairments, increased risk of falls, accidents and dependency. Melatonin receptors agonists are safe and effective drugs for primary insomnia and circadian rhythm sleep disorders and are potentially useful for cognition and sleep in. Piromelatine is a novel investigational MT1\MT2 and 5HT1A\D receptors agonist developed for primary and co-morbid insomnia. In Phase-I studies it demonstrated good oral bioavailability (Elimination half-life  $2.8 \pm 1.4$  hours), good safety & tolerability profile across a wide dose range and provided the first indication for beneficial effects on sleep maintenance. In a Phase-II study in insomnia patients, piromelatine demonstrated significant improvements in sleep maintenance based on objective assessments (polysomnography recorded wake after sleep onset, sleep efficiency and total sleep time) and good safety profile with no detrimental effects on next-day psychomotor performance and memory. The electroencephalographic (EEG) power spectral density (PSD) profile of piromelatine indicated significant reduction in beta power ( $p < 0.05$ ), a marker of cortical arousal and enhanced delta power ( $P < 0.05$ ), a marker of restorative sleep. In preclinical studies in rats, piromelatine enhanced memory performance, attenuated cellular loss and neuronal and cognitive impairment in intrahippocampal  $A\beta(1-42)$  injection-induced neurodegeneration and reversed memory, hippocampal BDNF, CREB and pCREB deficits and hippocampal neurogenesis in chronic mild stress rats. Such unique effects suggest that piromelatine is a promising drug candidate in insomnia patients and particularly those with comorbid MCI or AD.

### Biography

Nava Zisapel is Founder and Chief Scientific Officer of Neurim Pharmaceuticals, Ltd. She is a full Professor at Tel-Aviv University with a specialization in Neuro-biochemistry and holds the Michael Gluck Chair in Neuropharmacology and ALS Research, USA. He holds a BSc in Chemistry, an MS. in Biochemistry and a PhD in Biochemistry from Tel-Aviv University. She has authored, together with her students and other scientists, over 160 original research publications in peer-reviewed journals.

[navazis@post.tau.ac.il](mailto:navazis@post.tau.ac.il)

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