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Daridorexant

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Daridorexant belongs to a class of drugs known as dual orexin receptor (OX1R and OX2R) antagonists. It achieves its function by blocking the binding of wake-promoting neuropeptides orexins. This novel mechanism is believed to turn down overactive wakefulness and as we know so far, most other treatments for insomnia can be sedating. Insomnia disorder is defined as difficulty initiating or maintaining sleep, causing clinically significant distress or impairment in important areas of daytime functioning. It is important to mention that chronic insomnia disorder is one of the most prevalent sleep disorders in Europe, it affects between 6 and 12 % of the adult population. Along with daridorexant potent inhibition of orexin receptors, this molecule is also characterized by rapid absorption utilized for sleep onset and pharmacokinetic properties such that approximately 80 % is eliminated after night to help reduce any residual effects. Daridorexant is currently marketed in USA under the name Quviviq as it gained approval from U.S. Food and Drug Administration in doses of 25 and 50 mg [1-3]. Base of the approval is comprised from phase 3 trials. One hundred and sixty trial sites from 18 countries participated in those trials, involving almost two thousand adults suffering from insomnia. Clinical trials were characterized by inclusion of randomized individuals with insomnia that received either placebo or daridorexant in the evening, once per day during three months. In one study, 924 individuals were randomized to placebo, daridorexant 25 mg or daridorexant 10 mg, while another study had 930 participants randomized to placebo, daridorexant 50 mg or daridorexant 25 mg. A placebo run-out period in duration of 7 days was included at the termination of the 3-month treatment interval in aforementioned studies. Following this period participants had the option to enter a double blind and placebo controlled extension study which was carried out in duration of 9 months. Approximately 600 participants were treated cumulatively for at least 6 months, while 373 participants received treatment for minimally 12 months [2].

Changes from baseline to month 1 and month 3 in wake after sleep onset (used as a measure of sleep maintenance) and in Latency to Persistent Sleep (used to measure sleep induction) were primary efficacy endpoints for aforementioned studies. The measurement of endpoints was accomplished by polysomnography, which was conducted in a sleep laboratory. Patient-reported total sleep time was evaluated every morning at home with a validated sleep diary questionnaire and represented a secondary endpoint. In the first study, doses of 25 and 50 mg revealed a statistically significant improvement in measurements at month 1, 3, and against placebo. In the second study, dosing of 25 mg indicated statistically significant enhancement on wake after sleep onset and

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total sleep time when compared to placebo at interval of 1 month and interval of 3 months. The U.S. Food and Drug Administration did not approve the 10 mg dosing consequently to its lack of improvement on measurements. The 50 mg dose showed a statistically significant mitigation of daytime sleepiness when set side by side to placebo. The sleepiness domain score from the Insomnia Daytime Symptoms and Impacts Questionnaire at months 1 and 3 quantified this. Twenty-five milligram dose results did not have statistical significance at both time points in either study [2,4].

Regarding adverse events - somnolence, headache and fatigue were most frequently observed. Other side effects, such as hallucinations, complex sleep behaviours, sleep paralysis and worsening of depression were noted [4].

Daridorexant will be classified as a controlled substance by the U.S. Drug Enforcement Administration in line with the U.S. Food and Drug Administration recommendation. It is anticipated to reach the market in the middle of 2022 [2]. Daridorexant also received a positive opinion from the Committee for Medicinal Products of the European Medicines Agency for human use. However, at this moment it is unknown if it will be approved and when it will be available [4].

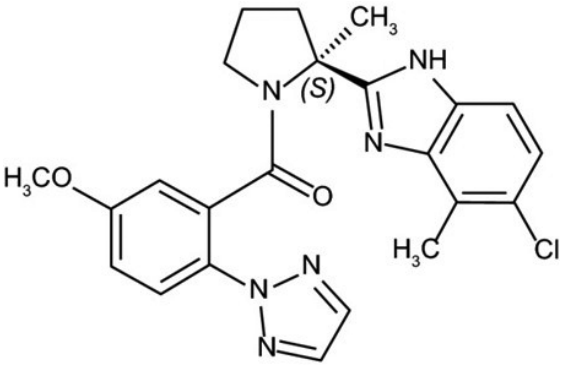

Figure 1. Chemical structure of daridorexant

All in all, sleep is the foundation of adequate physical and mental state and is also essential for optimal daytime functioning. Insomnia as a disorder does not only affect night-time but also has dramatic effects on daytime functioning and overall well-being. Daridorexant with its novel mechanism of action will hopefully satisfy some of medical requirements for insomnia management.

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