Media Release
May 3, 2022

Europe's first dual orexin receptor antagonist – QUVIVIQ (daridorexant) – granted approval to improve both nighttime symptoms and daytime functioning in adults with chronic insomnia disorder

- QUVIVIQ™▼ is indicated for the treatment of adult patients with insomnia characterized by symptoms present for at least three months and considerable impact on daytime functioning
- Comprehensive nighttime efficacy and unique daytime functioning data, together with a favorable safety profile, are included in the QUVIVIQ product label
- This approval makes QUVIVIQ, Europe's first dual orexin receptor antagonist, a new targeted mechanism of action that decreases overactive wakefulness in insomnia

Allschwil, Switzerland – May 3, 2022
Idorsia Ltd (SIX: IDIA) today announced the European Commission (EC) has granted marketing authorization for QUVIVIQ™▼ (daridorexant) for the treatment of adult patients with insomnia characterized by symptoms present for at least three months and considerable impact on daytime functioning.[1] Chronic insomnia disorder is one of the most prevalent sleep disorders in Europe, affecting between 6%-12% of the adult population,[2] and impacting both physical and mental health.[3,4]

With this approval, QUVIVIQ becomes the first dual orexin receptor antagonist (DORA) in the European Union (EU) for the treatment of insomnia. Rather than inducing sleep through broad inhibition of brain activity, QUVIVIQ blocks only the activation of orexin receptors.[1] Consequently, QUVIVIQ decreases the wake drive, allowing sleep to occur, without altering the proportion of sleep stages.1

The recommended dose of QUVIVIQ is one tablet of 50 mg once per night, taken orally in the evening within 30 minutes before going to bed.[1] In certain circumstances, such as patients with moderate hepatic impairment or who are taking moderate CYP3A4 inhibitors, the recommended dose is 25 mg once per night.[1]

Jean-Paul Clozel, MD and Chief Executive Officer of Idorsia, commented:
"As our first treatment authorized in the EU, the approval of QUVIVIQ marks a significant medical advancement in the management of insomnia and a big milestone for Idorsia. I am delighted to see the comprehensive long-term safety and efficacy data we have generated with QUVIVIQ included in an outstanding label. In particular, I'm pleased with the description of the unique daytime functioning improvement data, which I believe will revolutionize the way insomnia is treated in the EU. We are incredibly proud to bring the therapeutic benefits of QUVIVIQ, the first dual orexin receptor antagonist in Europe, to clinicians and patients. We expect to make it available in the first countries before the end of the year."

The EC decision is supported by robust Phase 3 results – recently published in The Lancet Neurology – which demonstrated that at the recommended dose, QUVIVIQ improved sleep onset, sleep maintenance and self-reported total sleep time in adults with chronic insomnia disorder.[5] A major focus of the trials was to evaluate the impact of QUVIVIQ on daytime functioning in patients with

insomnia disorder, as assessed by IDSIQ, a patient-reported outcomes instrument specifically developed and validated according to FDA guidelines, to measure daytime functioning in patients with insomnia. The recommended dose of QUVIVIQ demonstrated highly statistically significant improvement in the daytime sleepiness domain of IDSIQ, which means patients reported feeling less mentally and physically tired, less sleepy and more energetic during the day, at months one and three compared to placebo, with a favorable safety profile.1,5 In clinical trials, the most frequently reported adverse reactions were headache and somnolence.[1] The majority of adverse reactions were mild to moderate in intensity.[1] No evidence of a dose-relationship for the frequency or severity of adverse reactions was observed.[1] The adverse reaction profile in elderly patients was consistent with younger patients.[1] Somnolence was reported in 3% and 2% of patients treated with QUVIVIQ 25 mg and 50 mg, respectively, compared to 2% of subjects on placebo.[1] The marketing authorization was also supported by a long-term follow-up extension study, which together with the pivotal trials, provides clinical data for up to 12 months of continuous treatment.[1]

For more information on the marketing authorization of QUVIVIQ in the European Union, please review the Summary of Product Characteristics (SmPC).

Professor Damien Léger, Université Paris Cité, France, commented:
"Sleep is an essential pillar for good physical and mental health to ensure optimal functioning throughout the day. Chronic insomnia disorder is persistent in many patients and has direct consequences, such as impaired daytime function, decreased workplace productivity, injuries and accidents, making insomnia not only a disease of the night, but one that also markedly affects the day and a patient's well-being. QUVIVIQ, which can be used long-term, effectively improves sleep parameters and people's ability to function better during the day, while avoiding major safety concerns, fulfilling the major medical requirements for insomnia management. This is great news for the millions of adults and elderly people across the EU living with chronic insomnia."

About QUVIVIQ (daridorexant) in insomnia disorder
Studies over the past decades have shown that hyperarousal processes in the brain play a key role in the pathology of insomnia.[6] Chronic insomnia disorder is the result of continued brain hyperarousal that requires sustained management with therapy suitable for daily use over months.[7] Orexin is a neuropeptide, a small protein-like molecule, produced by the brain that promotes wakefulness.[1,6] QUVIVIQ reduces nocturnal hyperarousal to improve sleep (onset and maintenance) without next-morning residual effects in insomnia patients, and thus improve daytime functioning.[5]

Regulatory status of daridorexant
Marketing authorization of QUVIVIQ in Europe follows a positive opinion issued on 24 February by the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP). The approval is valid in all European Union Member States, as well as the European Economic Area countries Iceland, Liechtenstein and Norway, and Northern Ireland under the Northern Ireland Protocol. In Great Britain, a separate application for the use of daridorexant for the same indication has been submitted to the Medicines and Healthcare products Regulatory Agency (MHRA) via the European Commission Decision Reliance Procedure.

Daridorexant is currently under review with Swissmedic and Health Canada. In January 2022, QUVIVIQ (daridorexant) was approved by the US Food and Drug Administration (FDA) for the treatment of adult patients with insomnia, characterized by difficulties with sleep onset and/or sleep maintenance.[8]

Notes to the editor

About insomnia disorder

Insomnia disorder is defined as difficulty initiating or maintaining sleep, causing clinically significant distress or impairment in important areas of daytime functioning.[3] This impact on sleep quantity or quality should be present for at least three nights per week, lasts for at least three months, and occurs despite an adequate opportunity to sleep.[3]

Insomnia is a condition of overactive wake signaling and studies have shown that areas of the brain associated with wakefulness remain more active during sleep in patients with insomnia.[9,10] It is a common problem with an estimated prevalence in Europe of 6-12% of the adult population.[2]

Insomnia as a disorder is quite different from a brief period of poor sleep, and it can take its toll on both physical and mental health.[4] It is a persistent condition with a negative impact on daytime functioning.[3] Idorsia's research has shown that poor quality sleep can affect many aspects of daily life, including the ability to concentrate, mood, and energy levels.

The goal of treatments for insomnia is to improve sleep quality and quantity, as well as daytime functioning, while avoiding adverse events and next-morning residual effects.[5] Current recommended treatment of insomnia includes sleep hygiene therapy, cognitive behavioral therapy, and pharmacotherapy.[6]

About the orexin system

Wake and sleep signaling is regulated by intricate neural circuitry in the brain. One key component of this process is the orexin system, which helps promote wakefulness.[5,7,11] There are two forms of orexin neuropeptides – small protein-like molecules used by nerve cells (neurons) to communicate with each other in the brain – orexin A and orexin B.[7] Orexin promotes wakefulness through its receptors OX1R and OX2R.[7] Together, these neuropeptides and receptors make up the orexin system. The orexin system stimulates targeted neurons in the wake system – leading to the release of several chemicals (serotonin, histamine, acetylcholine, norepinephrine) – to promote wakefulness.[12] Under normal circumstances, orexin levels rise throughout the day as wakefulness is promoted and then fall at night.[13] Overactivity of the wake system is an important driver of insomnia.[5,10]

The daridorexant Phase 3 registration program

The Phase 3 registration program comprised two three-month studies, together with a long-term double-blind extension study.[1] The program enrolled a total of 1,854 patients with insomnia disorder.[1] As insomnia often presents later in life, and older adults are more susceptible to experience fragmented sleep, early awakening and daytime sleepiness,[14] around 40% of the recruited population was at least 65 years of age.[5]

The placebo-controlled studies investigated the effects of three doses of daridorexant (10 mg, 25 mg, and 50 mg) on sleep and daytime functioning parameters, objectively in a sleep lab by polysomnography and subjectively with a daily patient diary at home.[5] The impact of insomnia on patients' daytime functioning was measured daily using the sleepiness domain score from the Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ©) – a patient-reported outcome (PRO) instrument developed and validated according to the FDA Guidance for Industry.[5]

More than 800 patients continued treatment in the 40-week extension study, which measured the effect of all three doses vs. placebo, generating data for long-term treatment of insomnia disorder.[15]

Phase 3 data has been reported in The Lancet Neurology: The pivotal studies demonstrated that daridorexant 50 mg significantly improved sleep onset, sleep maintenance and self-reported total sleep time at months one and three compared to placebo.[5] The largest effect was observed with the highest dose (50 mg), followed by 25 mg, while the 10 mg dose did not have a significant effect.[5] In all treatment groups the proportions of sleep stages were preserved, in contrast to findings reported with benzodiazepine receptor agonists.[5]

A major focus of the trials was to evaluate the impact of daridorexant on daytime functioning in patients with insomnia disorder, as assessed by the IDSIQ.[5] IDSIQ is a patient-reported outcomes instrument specifically developed and validated according to FDA guidelines, to measure daytime functioning in patients with insomnia.[16] The sleepiness domain score of the IDSIQ was evaluated as a key secondary endpoint in both pivotal studies and comparisons to placebo included type I error control for multiplicity.[5] Daridorexant 50 mg demonstrated highly statistically significant improvement in daytime sleepiness at month one and month three.[5] The sleepiness domain score was not significantly improved on 25 mg in either study at either timepoint.[5]

The overall incidence of adverse events was comparable between treatment groups.[1] The most frequently reported adverse reactions were headache and somnolence and, overall, the majority of adverse reactions were mild to moderate in intensity.[1] There was no evidence of dose-dependent increases in adverse events across the dosing range.[1] Further, no dependence, rebound insomnia or evidence of abuse or withdrawal symptoms indicative of physical dependence upon treatment discontinuation was observed in clinical studies.[1]

Additional monitoring for QUVIVIQ™▼ (daridorexant)

▼ As a new medicinal product containing a new active substance, this medicinal product is subject to additional monitoring, and it is therefore important to report any suspected adverse events related to this medicinal product. Adverse events should be reported. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

Contraindications

- Hypersensitivity to daridorexant or any of the excipients
- Narcolepsy
- Concomitant use with strong CYP3A4 inhibitors

Warnings and precautions for use

Use with caution in elderly patients because of the general risk of falls. Efficacy and safety data in patients >75 are limited.

Patients should be cautioned about drinking alcohol during treatment.

Sleep paralysis and hypnagogic/hypnopompic hallucinations can occur, mainly during the first weeks of treatment. Symptoms similar to mild cataplexy have been reported with dual orexin receptor antagonists. Prescribers should explain this to patients and should consider discontinuing in case events occur.

Use with caution in patients exhibiting symptoms of depression.

Use with caution in patients with psychiatric co-morbidities due to limited efficacy and safety data.

Daridorexant did not have significant respiratory effects in patients with mild or moderate OSA or moderate COPD. In the absence of data, use with caution in patients with severe OSA and severe COPD.

There was no evidence of abuse or withdrawal symptoms indicative of physical dependence upon treatment discontinuation in clinical studies with daridorexant in subjects with insomnia. Because individuals with a history of abuse or addiction to alcohol or other substances may be at increased risk for abuse of QUVIVIQ, these patients should be followed carefully.

Use is not recommended in patients with severe hepatic impairment.

Effects on availability to drive and use machines

Patients should be cautioned about engaging in potentially hazardous activities, driving, or operating heavy machinery unless they feel fully alert, especially in the first few days of treatment. In order to minimize this risk, a period of approximately 9 hours is recommended between taking QUVIVIQ and driving or using machines.

About Professor Damien Léger

Professor Damien Léger, M.D, Ph.D. is the Head of the University Hospital Hôtel Dieu, APHP, Sleep and Vigilance Center in Paris, France. He is also Professor of Medicine at the Université Paris Cité. His primary research interests focus on the impact of sleep disorders on public health, and he serves as a consultant to the World Health Organization, the European Council, the European Department of Mobility, French National Health Agency and the French Ministry of Labor, Health, Transportation, Education and Environment, advising these institutions on the influence of environmental factors such as light, noise, shift and night work and work conditions on sleep and alertness. Professor Léger was President of the French Sleep Research and Medicine Society from 2017 to 2019, President of the French Institute of Sleep and Vigilance from 2010 to 2015 and is a member of the European Board of the European Insomnia Network. He is the author of eight books and over 220 scientific publications. Professor Léger serves as a consultant to Idorsia.

References

1 QUVIVIQ™ Summary of Product Characteristics. 2022.
2 Riemann, D., et al. Sleep. 2017;26(6):675-700.
3 The Diagnostic and Statistical Manual of Mental Disorders (5th ed.; DSM–5; American Psychiatric Association, 2013).
4 Wardle-Pinkston S., et al. Sleep Med Rev. 2019;48.
5 Mignot, E., et al. Lancet Neurol. 2022;21:125–39.
6 Muehlan, C., et al. Expert Opin. Drug Metab. Toxicol. 2020;16(11):1063–1078.
7 Muehlan, C., et al. J Psychopharmacol. 2020;34(3):326-335.
8 QUVIVIQ Prescribing Information. Idorsia Pharmaceuticals US Inc. Jan 2022.

[9] Buysse, D.J., et al. Drug Discov Today Dis Models. 2011;8(4):129-137.
[10] Levenson, J.C., et al. Chest. 2015;147(4):1179-1192.
[11] Boof, M.L., et al. Eur J Clin Pharmacol. 2019;75(2):195-205.
[12] Clifford, B.S., et al. Trends Neurosci. 2001;24(12).726-31.
[13] Gotter, A.L., et al. BMC Neuroscience. 2013;14(1):14-19.
[14] Patel, D., et al. J Clin Sleep Med. 2018;14(06):1017–1024.
[15] Data on file, Idorsia.
[16] Hudgens, S., et al. Patient. 2020. doi:10.1007/s40271-020-00474-z.

About Idorsia

Idorsia Ltd is reaching out for more – We have more ideas, we see more opportunities and we want to help more patients. In order to achieve this, we will develop Idorsia into a leading biopharmaceutical company, with a strong scientific core.

Headquartered near Basel, Switzerland – a European biotech-hub – Idorsia is specialized in the discovery, development and commercialization of small molecules to transform the horizon of therapeutic options. Idorsia has a broad portfolio of innovative drugs in the pipeline, an experienced team of professionals covering all disciplines from bench to bedside, state-of-the-art facilities, and a strong balance sheet – the ideal constellation to translate R&D efforts into business success.

Idorsia was listed on the SIX Swiss Exchange (ticker symbol: IDIA) in June 2017 and has over 1,200 highly qualified specialists dedicated to realizing our ambitious targets.

For further information, please contact

Andrew C. Weiss
Senior Vice President, Head of Investor Relations & Corporate Communications
Idorsia Pharmaceuticals Ltd, Hegenheimermattweg 91, CH-4123 Allschwil
+41 58 844 10 10
investor.relations@idorsia.com – media.relations@idorsia.com – www.idorsia.com

The above information contains certain "forward-looking statements", relating to the company's business, which can be identified by the use of forward-looking terminology such as "estimates", "believes", "expects", "may", "are expected to", "will", "will continue", "should", "would be", "seeks", "pending" or "anticipates" or similar expressions, or by discussions of strategy, plans or intentions. Such statements include descriptions of the company's investment and research and development programs and anticipated expenditures in connection therewith, descriptions of new products expected to be introduced by the company and anticipated customer demand for such products and products in the company's existing portfolio. Such statements reflect the current views of the company with respect to future events and are subject to certain risks, uncertainties and assumptions. Many factors could cause the actual results, performance or achievements of the company to be materially different from any future results, performances or achievements that may be expressed or implied by such forward-looking statements. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those described herein as anticipated, believed, estimated or expected.