Review Article

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A Review on Daridorexant: Pharmacological, Pharmacodynamic and Pharmacokinetic Profile

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Abstract

Daridorexant, a double orexin type 1 and type 2 (OX1 and OX2) receptor antagonist (DORA), has been recently introduced in the market for the treatment of insomnia. DORAs are a new form of sleep drugs that can be used instead of standard positive allosteric gamma-amino butyric acid (GABA)-A receptor modulators. Daridorexant blocks the effects of the wake promoting orexin (also known as hypocretin) neuropeptides by binding specifically to both orexin receptors. This approach avoids the extensive inhibition of neuronal circuits that positive allosteric GABA-A receptor modulators cause, as well as the related adverse effects. In this reviewdetailed Pharmacology of Daridorexant including its mechanism of action, Pharmacodynamics, and Pharmacokinetics have been compiled.

Keywords: Orexin; GABA; Sleep disorder; Nemorexant.

INTRODUCTION

Insomnia is a prevalent sleep condition that has a number of complications as well as significant economic and social consequences. About 5–20 percent of the adult population suffers from chronic insomnia.[1,2] According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) Insomnia can be characterized as "Disappointment with the amount or nature of rest, as well as inconvenience starting or supporting rest or getting up promptly in the first part of the day. These symptoms appear at least three times each week and last at least three months.[3] It's actually important that the DSM-5 has supplanted the differentiation among essential and optional sleep deprivation by presenting sleep deprivation jumble as an umbrella classification that incorporates evening side effects like delayed rest beginning inactivity, challengeswith rest support, and early daytime arousing, as well as daytime disability like weakness, decreased consideration, mind-set aggravation, or other huge regions.[3] Sleep deprivation medicines focus on the GABA-A, serotonin, receptor, or melatonin receptors. Positive allosteric prescriptions (zopiclone, zolpidem, and zaleplon: 'Z'-drugs) The most frequently utilized hypnotics, GABA-A subunit alpha 1 receptor modulators, incite rest by creating a wide concealment of focal sensory system (CNS) movement.[4] Benzodiazepines (BZD), 'Z'-drugs, melatonin receptor agonists, and sedating antidepressants are some of the most often

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utilised pharmaceutical alternatives for insomnia.[5] In spite of their viability, these medications can cause different unfavourable impacts, including following day remaining sluggishness, engine incoordination, falls, memory and mental weakness, and the gamble of fixation, reliance, and resilience, all of which should be considered while using them.[6-8] Furthermore, presently available sleep drugs that effectively treat sleep maintenance issues may be accompanied with typical somnolence and sleepiness adverse effects.[9] As a result, the pharmacodynamic effectiveness of sleep medicines must be balanced against the possibility for lingering effects. The discovery of the wakefulness orexin (hypocretin) signalling pathway has led to the development of orexin receptor antagonists as potential therapeutics1. The orexin (otherwise called hypocretin) frame work has as of late been distinguished as a likely objective for the production of another kind of rest medication. It was observed for the first time in 2007 that Almorexant, a double orexin receptor antagonist (DORA), upgraded snooze rodents, canines, and healthy subjects.[10]

Daridorexant: Key Points

- On January 7, 2020, it received its first approval in the United States.
- Licensed for use in individuals with insomnia that is characterised by problems with onset or upkeep of sleep.
- Idorsia Pharmaceutical Ltd. is dealing with a double orexin receptor antagonist for the treatment of a sleeping disorder.

Addressing the G protein-coupled receptors OX1 and OX2, which are highly expressed in the brain, daridorexant is a dual orexin type 1 and type 2 receptor antagonist (DORA) being researched for the treatment of insomnia.[1] Through their interactions with OX1 and OX2, the hypothalamus endogenous ligands orexin A and orexin B (also known as hypocre-tin-1 and -2) promote wakefulness.[11] Research in creating orexin antagonists as an effective treatment for insomnia was prompted by the discoveries that narcolepsy is associated with a reduction in orexin-producing neurons and that inhibiting both OX1 and OX2 improves sleep patterns.[12] Because it had a half-life and an expected action duration of less than 8 hours at a dosage of 25 mg, Daridorexant was selected from a pool of pharmacological possibilities that was designed to minimise residual effects that might affect daytime functioning. The medicine has been authorised in the United States.[13] It has also got approval from the European Commission's Committee for Medicinal Products for Human Use (CHMP). (https://www.ema.europa.eu/en/news/meeting-highlights-committee-medicinal-products-human-use-chmp-21-24-february-2022). Daridorexant(brand name Quviviq) is prescribed at a dose of 25–50 mg once each night, given within 30 minutes of going to bed and at least 7 hours before anticipated wakeup.[14] Daytime impairment, which is more likely when Daridorexant is used with other CNS depressants, exacerbation of depression or suicidal thoughts, sleep paralysis, hypnagogic/hypnopompic hallucinations, and symptoms similar to cataplexy are all possible side effects and are all mentioned in the US prescribing information. Daridorexant use may also result in complex sleep behaviours such sleepwalking, sleep driving, and engaging in other activities while not fully awake. If this happens, the medication should be stopped immediately. It is also important to consider how the medicine affects respiratory capacity.[13]

CHEMISTRY[2,15]

Daridorexant, also known as Nemorexant, is a benzimidazole derivative (Figure 1). Its chemical name is (S)-(2-(5-chloro-4-methyl-1H-benzo [d] imidazol-2-yl)-2-methylpyrrolidin-1-yl)(5-methoxy-2-(2H-1,2,3-triazol-2-yl)phenyl) methanone. Its molecular weight is 450.93 g/mol (or 487.38 g/mol for the hydrochloride), and chemical formula is $C_{23}H_{23}N_6O_2Cl$. Daridorexant hydrochloride is a white to light yellowish powder that is water soluble.

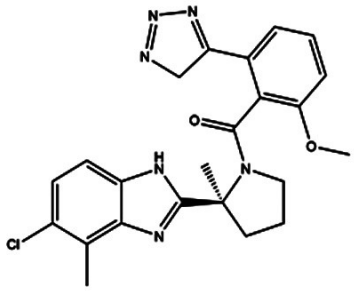

Fig. 1: Chemical structure of Daridorexant.

PHARMACOLOGY

Mechanism of Action

Complex interplay between wake-promoting systems and sleep-promoting systems, such as inhibitory GABA activity, such as orexins, acetylcholine, and monoaminergic systems, govern

the sleep-wake cycle.[16] A tiny group of neurons in the lateral hypothalamus generate orexin, also known as hypocretin, a wake-promoting neuropeptide. Orexin maintains a wake by activating orexin neurons that are most active during active wakefulness and have the least activity during sleep 2. The wake-promoting neurons that project to orexin include cholinergic neurons of the basal forebrain, the pedunculopontine, and the laterodorsal tegmental nuclei, as well as histaminergic neurons of the tuber mammillary nucleus, noradrenergic neurons of the locus coeruleus, serotoninergic neurons of the dorsal raphe, and dopaminergic neurons of the ventral.[2] These wake-promoting neurons are part of the ascending reticular activating system, which works in a sleep-wake cycle feedback loop.[17] Orexin type 1 and 2 receptors (OX1R and OX2R), which are G-protein coupled receptors, bind to two different forms of orexin (OXA and OXB). OXA primarily binds to OX1R, whereas OX2R has a dual affinity for both OXA and OXB.[17] The precise function of each orexin receptor is unknown; however, evidence suggests that OX2R modulates sleep and wakefulness, whereas OX1R plays a role in sleep maintenance.[16] By preventing the binding of the wake-promoting neuropeptides OXA and OXB to OX1R and OX2R, the drug Daridorexant reduces wake drive.[15] Daridorexant preferentially targets orexin neurons and inhibits downstream neuronal pathways that promote wakefulness, but it has no effect on neuronal pathways that induce adverse effects found with positive allosteric GABA-A receptor modulators 2.

PHARMACODYNAMICS

In vitro experiments with Daridorexant revealed receptor occupancy half-lives of 8 and 4 minutes and inhibition constants (Kb) of 0.52 nM and 0.78 nM for human OX1 and OX2 receptors, respectively.[18] As given orally to rats, Daridorexant 30 mg/kg caused the same proportions of non-REM and REM sleep to total sleep time, a 22 percent decrease in active waking time, and 29 and 84 percent increases in non-REM and REM sleep, respectively, when compared to vehicle. The medicine was also associated with notable decreases in the latency to both REM and sustained non-REM sleep.[18] Daridorexant is a potent and specific small-molecule dual OX1R and OX2R antagonist. With apparent Kb values of 1.1, 0.3, and 0.5 nM at OX1R and 1.7, 0.7, and 0.8 nM at OX2R in rats, dogs, and humans, respectively, daridorexant functions as a competitive, orthosteric antagonist in intracellular Ca2+ release assays18. Therefore, daridorexant works just as well against OX1R and OX2R. Daridorexant shown no significant in vitro activity in a panel screen of more than 130 central and peripheral pharmacological targets other than orexin receptors, including GABA receptors and other brain targets associated with the risk of addiction 2. In rats and dogs, Daridorexant is orally accessible and successfully crosses the blood–brain barrier 2. Within 1 hour of giving male volunteers single ascending doses of Daridorexant, they showed obvious CNS effects (e.g., lower alertness, attentiveness, vasomotor coordination, and postural stability). The effects of dosages up to 100 mg peaked 1.5 hours after delivery, with 25 mg and 50 mg doses having effects that returned to baseline 3-6 and 6-8 hours, respectively, after administration.[12] On day 1 and day 5, participants who received repeated 25 and 75 mg daily doses of Daridorexant showed decreased alertness and attention, as well as vasomotor coordination and postural stability, as compared to placebo. The effects peaked at 2 hours after injection and faded to baseline between 4–10 hours.[19]

PHARMACOKINETICS

Daridorexant has dose proportionate plasma exposure at dosages of 25–50 mg. Following administration of both repeated doses and a single dosage, the drug's pharmacokinetic profile is the same, and there is no evidence of accumulation, with peak plasma concentrations reaching in 1–2 hours (tmax). A high-fat/high-calorie lunch delayed Daridorexant tmax by 1.3 hours and lowered Cmax by 16% in participants, but had no effect on total exposure (AUC). The medication is 99.7% bound to plasma proteins and has a volume of distribution of 31 L. The terminal half-life (t12) of Daridorexant was 8 hours in all experiments.[14] Daridorexant is extensively metabolised, predominantly by CYP3A4 (89 percent), and mostly eliminated as metabolites in the faeces (57 percent) and urine (28 percent).[20] Age, sex, race, body size, or mild to severe renal impairment (Cockcroft-Gault 30 ml/ min, not on dialysis) had no clinically relevant effect on Daridorexant pharmacokinetic parameters.[21] Because moderate (Child-Pugh B) but not mild (Child-Pugh A) hepatic impairment has been proven to lengthen the t1/2 of Daridorexant, the highest dosage suggested in individuals with Child-Pugh B impairment is 25 mg once per night.[22] Daridorexant 50 mg can be given with famotidine, a histamine 2 receptor inhibitor, without any dosage adjustments.[23] The combination of Daridorexant 50 mg and the SSRI Citalopram did not result in clinically significant pharmacokinetic alterations24.

The pharmacokinetics of Rosuvastatin were unaffected by Daridorexant co-administration, demonstrating that Daridorexant can be safely coadministered with BCRP substrates without dose modifications.[25] Co-administration of Daridorexant 25mg with the moderate CYP3A4 inhibitor Diltiazem increased Daridorexant AUC by 240 percent, and co-administration with the strong CYP3A4 inhibitor Itraconazole is expected to increase Daridorexant AUC by > 400 percent, according to physiologically-based pharmacokinetic modelling. (https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2022/214985Orig1s000ltr.pdf).

ABSORPTION

Daridorexant reaches maximal plasma concentrations in one to two hours. Absolute bioavailability for Daridorexant is 62%. A high-fat, high-calorie meal delayed Tmax by 1.3 hours and decreased Cmax by 16% in healthy subjects, but the overall exposure (AUC) was unaltered.[15]

DISTRIBUTION

Distribution volume of Daridorexant is 31 L. It binds to plasma proteins; 99.7%. Plasma to blood ratio is 0.64for Daridorexant 15. It effectively crosses the blood-brain barrier (BBB).[26]

ELIMINATION

Majority of Daridorexant (57 percent) is excreted in faecesfollowed by in urine (28 percent). Just tiny amounts of the original substance are present since it is primarily removed as metabolites.[15] The half-life of the medication is around 8 hours, or 6 to 10 hours in the body. Suvorexant (12 hours) and lemborexant (18-55 hours), two other orexin receptor antagonists, have a shorter half-life3. The short half-life of Daridorexant could make daytime sedation less necessary.[27]

INTERACTIONS

Both CYP3A4 inducers and inhibitors, such as Efavirenz and Ranitidine, can enhance or decrease Daridorexant exposure. It should not be used concurrently with strong CYP3A4 inhibitors or moderate to strong CYP3A4 inducers, and its maximum dosage should be decreased while using moderate CYP3A4 inhibitors. Daridorexant peak levels can be decreased without affecting total exposure by using gastric pH modifiers like Famotidine. Daridorexant doesn't appear to have any significant pharmacokinetic interactions with either alcohol or SSRIs like Citalopram. The risk of central nervous system depression and daytime impairment rises when Daridorexant is used with other sedatives such benzodiazepines, opioids, tricyclic antidepressants, and alcohol. It has not been demonstrated that other medications, including the SSRI Citalopram, Midazolam (a CYP3A4 substrate), Rosuvastatin (a BCRP substrate), and others significantly affect the pharmacokinetics of Daridorexant.[15]

In light of this, the maximum dosage of Daridorexant that is advised for use in conjunction with a moderate CYP3A4 inhibitor is 25 mg, and it is not advised to combine Daridorexant with a strong CYP3A4 inhibitor or a moderate or strong CYP3A4 inducer.[13] When paired with alcohol, Daridorexant Tmax was prolonged, and this was associated with cumulative effects on psychomotor function. Due to this, patients are advised not to consume alcohol while using Daridorexant.

CONCLUSION

The current pharmaceutical alternatives for chronic insomnia therapy do not suit the demands of all individuals. A possible treatment strategy is to target the orexin system. Daridorexant, a double orexin type 1 and type 2 receptor antagonist (DORA), was developed as a result of a lengthy drug development efforts with improved effectiveness, pharmacokinetic profile and reduced side effect. Daridorexant, like other DORAs, is predicted to sustain cognitive function, have a limited potential for misuse, and not cause tolerance or rebound after long-term usage, addressing many of the drawbacks of sleep medicines.

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