▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the “Undesirable effects” section for advice on the reporting of adverse reactions.

QUVIVIQ film-coated tablets

Composition

Active substances

Daridorexant (daridorexant hydrochloride)

Excipients

Tablet core: Mannitol, Microcrystalline cellulose, Povidone K 30, Croscarmellose sodium, highly dispersed Silicon dioxide, Magnesium stearate.
Film coat: Hypromellose, Microcrystalline cellulose, Glycerol, Talc, Titanium dioxide, Iron oxide yellow (50 mg tablets only), Iron oxide red, Iron oxide black.

1 tablet contains 0.655 mg sodium.

Pharmaceutical form and active substance quantity per unit

QUVIVIQ 25 mg film-coated tablets
Each film-coated tablet contains daridorexant hydrochloride equivalent to 25 mg of daridorexant.
Light purple arc-triangle shaped film-coated tablets, debossed with ‘25’ on one side, and ‘i’ on the other side.

QUVIVIQ 50 mg film-coated tablets
Each film-coated tablet contains daridorexant hydrochloride equivalent to 50 mg of daridorexant.
Light orange arc-triangle shaped film-coated tablets, debossed with ‘50’ on one side, and ‘i’ on the other side.

Indications/Uses

QUVIVIQ is indicated for the treatment of adult patients with insomnia, characterised by symptoms present for at least 3 months and considerable impact on daytime functioning.

Dosage/Administration

The recommended dose for adults is one tablet of 50 mg once per night, taken orally in the evening within 30 minutes before going to bed. Based on clinical judgement, some patients may be treated with 25 mg once per night (see Section Warnings and Precautions and Section Interactions).
The maximum daily dose is 50 mg.

Duration of treatment

The treatment duration should be as short as possible. After 3 months, the appropriateness of continued treatment should be reassessed and periodically thereafter.
Clinical data are available for up to 12 months of continuous treatment.
Treatment can be stopped without down-titration.

Patients with hepatic disorders

In patients with mild hepatic impairment (Child-Pugh score 5–6), no dose adjustment is required (see Section Pharmacokinetics).
The recommended dose of QUVIVIQ in patients with moderate hepatic impairment (Child-Pugh score 7–9) is one tablet of 25 mg once per night (see Section Pharmacokinetics).
In patients with severe hepatic impairment (Child-Pugh score ≥ 10), QUVIVIQ has not been studied and is not recommended (see Section Pharmacokinetics).

Patients with renal disorders

In patients with renal impairment (including severe), no dose adjustment is required (see Section Pharmacokinetics).

Elderly

No dose adjustment is required in elderly patients (> 65 years). Limited data are available in patients older than 75 years. No data are available in patients older than 85 years.

Children and adolescents

The safety and efficacy in paediatrics have not been studied.
QUVIVIQ is not indicated in paediatrics.

Dose adjustments due to interactions

<u>Co-administration with moderate CYP3A4 inhibitors</u>
The recommended dose when used with moderate CYP3A4 inhibitors is one tablet of 25 mg once per night (see Section Interactions).
The consumption of grapefruit or grapefruit juice in the evening should be avoided.

<u>Co-administration with CNS depressants</u>
In the case of co-administration with CNS-depressant drugs, dose adjustments of QUVIVIQ and/or the other drug(s) may be required, based on clinical evaluation, due to potentially additive effects (see Section Warnings and precautions and Section Interactions).

Mode of administration

QUVIVIQ can be taken with or without food, however sleep onset might be delayed if taken with or soon after a high-fat and high-calorie meal (see Section Pharmacokinetics).

Missed dose

If a patient forgets to take QUVIVIQ at bedtime, that dose should not be taken during the night.

Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed above.
- Narcolepsy.
- Concomitant use with strong CYP3A4 inhibitors (see Section Interactions).

Warnings and precautions

Elderly

Because of the general risk of falls in the elderly, daridorexant should be used with caution in this population, although clinical studies did not show an increase in the incidence of falls on daridorexant compared to placebo.
QUVIVIQ should be administered with caution in patients older than 75 years since efficacy and safety data in this population are limited.

CNS-depressant effects

Because daridorexant acts by reducing wakefulness, patients should be cautioned about engaging in potentially hazardous activities, driving, or operating heavy machinery unless they feel fully alert (see Section Effects on ability to drive and use machines).
Caution should be exercised when prescribing QUVIVIQ concomitantly with CNS-depressant medications due to potentially additive effects, and a dose adjustment of either QUVIVIQ or the concomitant CNS depressants should be considered.
Patients should be advised not to consume alcohol in combination with QUVIVIQ because of additive effects on psychomotor performance (see Section Interactions).

Sleep paralysis, hallucinations and cataplexy-like symptoms

Sleep paralysis, an inability to move or speak for up to several minutes during sleep-wake transitions, and hypnagogic/hypnopompic hallucinations, including vivid and disturbing perceptions, can occur with daridorexant.
Symptoms similar to mild cataplexy have been reported with dual orexin receptor antagonists.
Prescribers should explain the nature of these events to patients when prescribing QUVIVIQ.

Complex sleep behaviours

Complex sleep patterns have been reported to occur with the use of hypnotics (including orexin receptor antagonists such as QUVIVIQ). These behaviours include, for example, sleep-walking, sleep-driving, and engaging in other activities while not fully awake (preparing and eating food, making phone calls, having sex). Patients usually do not remember these events. Complex sleep behaviours may occur following the first or any subsequent use of a hypnotic, with or without the concomitant use of alcohol or CNS-depressant drugs. Treatment with QUVIVIQ should be discontinued immediately if complex sleep behaviours occur.

Worsening of depression and suicidal ideation

In primarily depressed patients treated with hypnotics, worsening of depression and suicidal thoughts and actions have been reported. As with other hypnotics, QUVIVIQ should be administered with caution in patients exhibiting symptoms of depression.

Isolated cases of suicidal ideation have been reported in Phase 3 clinical trials (1 case on daridorexant 10 mg, 1 case on 25 mg, 1 case on 50 mg, and 1 case on placebo; the 3 events reported on daridorexant were in subjects with pre-existing psychiatric conditions). Suicidal tendencies may be present in patients with depression and protective measures may be required.

Patients with psychiatric and neurological co-morbidities

Only a small number of patients with psychiatric co-morbidities were included in the Phase 3 clinical trials. Patients with acute and unstable psychiatric and somatic conditions, alcohol or substance abuse disorders, restless legs syndrome, circadian rhythm disorder, rapid eye movement (REM) sleep behaviour disorder, or narcolepsy were excluded from the pivotal studies. Furthermore, no patients with Parkinson’s, Alzheimer’s or Huntington’s disease were included in these studies. QUVIVIQ should be administered with caution in patients with unstable psychiatric or neurological co-morbidities since the efficacy and safety of QUVIVIQ have not been studied in these patients.

Patients with compromised respiratory function

In a study of patients with mild or moderate obstructive sleep apnoea (OSA; apnoea-hypopnoea index 5 to < 30 events per hour of sleep), daridorexant did not increase the frequency of apnoea/hypopnoea events and did not cause oxygen desaturation. Daridorexant has not been studied in patients with severe OSA (apnoea-hypopnoea index ≥ 30 events per hour).

In a study of patients with moderate chronic obstructive pulmonary disease (COPD; FEV1/FVC ratio ≤ 70% and 40% ≤ FEV1 < 80% of predicted), daridorexant did not cause oxygen desaturation. Daridorexant has not been studied in patients with severe COPD (FEV1 < 40% of predicted).

Caution should be exercised when prescribing QUVIVIQ to patients with severe OSA and severe COPD.

Hepatic impairment

Use is not recommended in patients with severe hepatic impairment (see Section Dosage/Administration and Section Pharmacokinetics).

Potential for drug abuse

In a Phase 1 study conducted in 72 recreational sedative drugs users, the effect of single-dose administration of daridorexant (therapeutic dose of 50 mg, doses of 100 mg and 150 mg), zolpidem (30 mg), suvorexant (150 mg), and placebo on subjective rating of “drug liking” was evaluated.
At the therapeutic dose of 50 mg, daridorexant showed significantly lower “drug liking” ratings than supratherapeutic dosages of zolpidem (30 mg) and suvorexant (150 mg). At supratherapeutic doses of 100 mg and 150 mg, daridorexant showed similar “drug liking” ratings to zolpidem (30 mg) and suvorexant (150 mg). Higher “drug liking” was observed with daridorexant, zolpidem and suvorexant compared to placebo.
In placebo-controlled Phase 3 clinical studies in which 1232 subjects with insomnia were treated with daridorexant for up to 12 months, there was no indication of any drug abuse potential.
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.

Investigations for withdrawal symptoms and rebound insomnia

In the Phase 3 clinical studies, no rebound insomnia and withdrawal symptoms upon treatment discontinuation of daridorexant were observed. Rebound was investigated objectively by polysomnography one day after the end of treatment and subjectively by sleep diary for 7 days after the end of treatment. Possible withdrawal symptoms were assessed by the BWSQ after 7 days and by AE reporting up to 30 days after the end of treatment. There is currently insufficient information on rebound insomnia or on withdrawal symptoms that could occur later than investigated in the Phase 3 clinical studies.

Excipients of particular interest

Sodium

QUVIVIQ contains less than 1 mmol sodium (23 mg) per film-coated tablet, i.e., it is essentially “sodium-free”.

Interactions

Effect of other agents on the pharmacokinetics of daridorexant

CYP3A4 inhibitors

In healthy subjects, co-administration of daridorexant 25 mg with the moderate CYP3A4 inhibitor diltiazem (240 mg once daily) increased daridorexant exposure parameters AUC and C_{max} by 2.4 times

and 1.4 times, respectively. In patients taking moderate CYP3A4 inhibitors (e.g., erythromycin, ciprofloxacin, cyclosporine), the recommended dose of QUVIVIQ is 25 mg.
No clinical study was conducted with a strong CYP3A4 inhibitor. Concomitant use of QUVIVIQ with strong inhibitors of CYP3A4 (e.g., itraconazole, clarithromycin, ritonavir) is contraindicated (see Section Contraindications).
The consumption of grapefruit or grapefruit juice in the evening should be avoided.

CYP3A4 inducers

In healthy subjects, co-administration with efavirenz (600 mg o.d.), a moderate CYP3A4 inducer, decreased daridorexant exposure parameters AUC and C_{max} by 61% and 35%, respectively.
Based on these results, concomitant use with a moderate or strong CYP3A4 inducer substantially decreases exposure to QUVIVIQ, which may reduce efficacy.

Gastric pH-modifiers

The solubility of daridorexant is pH-dependent. In healthy subjects, co-administration with famotidine (40 mg), an inhibitor of gastric acid secretion, decreased daridorexant C_{max} by approximately 39% while AUC remained unchanged.
No dose adjustment is required when QUVIVIQ is used concomitantly with treatments that reduce gastric acidity.

Alcohol

In healthy subjects, co-administration with alcohol did not lead to relevant effects on the PK of 50 mg daridorexant.

Citalopram

In healthy subjects, co-administration of 20 mg citalopram, a selective serotonin re-uptake inhibitor (SSRI), did not have any clinically relevant effect on the PK of 50 mg daridorexant.

Effect of daridorexant on the pharmacokinetics of other agents

CYP substrates

Daridorexant inhibits several CYP enzymes in vitro. The strongest inhibition was seen on CYP3A4 with a Ki of 4.6–4.8 µM. Inhibition of CYP2C8, CYP2C9, and CYP2C19 was less pronounced, with IC_{50} values in the range of 8.2–19 µM. Daridorexant induces CYP3A4 mRNA expression in human hepatocytes with an EC_{50} of 2.3 µM and, to a lesser extent, CYP2C9 and CYP2B6. Up-regulation of all CYP enzymes is mediated via activation of the PXR receptor with an EC_{50} of 2.3 µM. Daridorexant does not induce CYP1A2.
In a clinical study conducted in healthy subjects receiving daridorexant and midazolam, a sensitive CYP3A4 substrate, daridorexant at a dose of 25 mg (steady state) did not affect the PK of midazolam

(decrease of C_{max} and AUC_{0-24} by 6% and 2%, respectively), indicating an absence of CYP3A4 induction or inhibition at this dose. In a clinical study conducted in healthy subjects receiving 50 mg daridorexant and midazolam, exposure (AUC) to midazolam increased by 42%, indicating a mild CYP3A4 inhibition. Simultaneous administration of 50 mg QUVIVIQ with sensitive CYP3A4 substrates with a narrow therapeutic index (e.g., high-dose simvastatin, tacrolimus) should be handled with caution. In the same study, when daridorexant was administered for 7 days, no sign of CYP3A4 induction was detected.
In a clinical study conducted in healthy subjects receiving daridorexant and warfarin, a sensitive CYP2C9 substrate, daridorexant at a dose of 50 mg did not affect the PK and PD of warfarin, indicating an absence of effect on CYP2C9. CYP2C9 substrates can be administered with QUVIVIQ without dose adjustment.

Drug transport substrates

Based on in vitro studies, daridorexant is an inhibitor of several drug transport proteins, with the strongest inhibition seen on BCRP with IC_{50} value of 3.0 µM. Inhibition of other drug transport proteins including OATP1B1, OATP1B3, OAT3, OCT1, MATE-2K and MATE1 and P-gp/MDR1 was less pronounced, with IC_{50} values ranging from 8.4–71 µM. No inhibition was observed on OAT1 and OCT2.
In clinical studies conducted in healthy subjects receiving 25 mg and 50 mg daridorexant and rosuvastatin, a BCRP substrate, daridorexant did not affect the PK of rosuvastatin indicating an absence of inhibition of BCRP. BCRP substrates can be administered with QUVIVIQ without dose adjustment.
In a clinical study conducted in healthy subjects receiving daridorexant 50 mg and dabigatran etexilate, a sensitive P-gp substrate, dabigatran AUC and C_{max} increased by 42% and 29%, respectively, indicating a mild P-gp inhibition. Simultaneous administration of QUVIVIQ with P-gp substrates with a narrow therapeutic index (e.g., digoxin) should be handled with caution.

Alcohol

In healthy subjects, concomitant intake with alcohol led to a prolonged absorption of daridorexant (t_{max} increased by 1.25 h). Daridorexant exposure (C_{max} and AUC) and $t_{½}$ were unchanged.

Citalopram

In healthy subjects, the PK of citalopram at steady state was not affected by co-administration of 50 mg daridorexant.

Pharmacodynamic interactions

Alcohol

Co-administration of 50 mg daridorexant with alcohol led to additive effects on psychomotor performance.

Citalopram

No relevant interaction on psychomotor performance was observed when 50 mg daridorexant was co-administered with 20 mg citalopram in healthy subjects at steady state.

Pregnancy and lactation

Pregnancy

There are no data on the use of daridorexant in pregnant women. Animal studies did not indicate harmful effects with respect to reproductive toxicity (see “Preclinical data”).
QUVIVIQ should be used during pregnancy only if the clinical condition of the pregnant woman requires treatment with daridorexant.

Lactation

There are no data on the presence of daridorexant or its metabolites in human breast milk. Animal studies have shown the presence of daridorexant and its metabolites in milk.
A decision must be made whether to discontinue breast-feeding or to discontinue QUVIVIQ therapy. Both the benefit of breast-feeding for the child and the medical need for the mother to receive QUVIVIQ should be taken into account. Breastfed infants whose mother is taking daridorexant should be monitored for excessive somnolence.

Fertility

There are no data concerning the effect of exposure to daridorexant on human fertility. Animal studies have shown no impairment of fertility (see “Preclinical data”).

Effects on ability to drive and use machines

Hypnotics have a major influence on the ability to drive and use machines.
A randomised, double-blind, placebo- and active-controlled, four-way cross-over study evaluated the effects of nighttime administration of daridorexant on next-morning driving performance, using a driving simulator, 9 hours after dosing in healthy subjects aged from 50 to 79 years. Testing was conducted after one night (initial dosing) and after 4 consecutive nights of treatment with daridorexant 50 and 100 mg. Zopiclone 7.5 mg was used as an active comparator.
In the morning after first-dose administration, daridorexant impaired simulated driving performance as measured by the Standard Deviation of Lateral Position (SDLP). The effect was less pronounced with 50 mg than with 100 mg daridorexant. For both doses, no effect on driving performance was detected after 4 consecutive nights of administration. Zopiclone significantly impaired simulated driving performance at both time points.

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 (see Section Warnings and precautions). In order to minimise this risk, a period of approximately 9 hours is recommended between taking QUVIVIQ and driving or using machines.

Undesirable effects

The safety of daridorexant was evaluated in three placebo-controlled Phase 3 clinical studies (two 3-month confirmatory studies of identical design [Study 1 and Study 2], and a 9-month extension study [Study 3]). Study 1 included the 50 and 25 mg doses of daridorexant, while Study 2 included 25 and 10 mg daridorexant. A total of 1847 subjects (including approximately 40% elderly subjects [≥ 65 years old]), received daridorexant 50 mg (N = 308); 25 mg (N = 618); or 10 mg (N = 306) or placebo (N = 615). A total of 576 subjects were treated with daridorexant for at least 6 months and 331 for at least 12 months.

Summary of safety profile

The most frequently reported adverse reactions (in at least 2% of subjects and with a > 1% difference vs placebo) during double-blind treatment of Study 1 and Study 2 were headache (6%, 5% and 4% on daridorexant 50 mg, 25 mg and placebo, respectively) and somnolence (2%, 3% and 2% on daridorexant 50 mg, 25 mg and placebo, respectively).
Most adverse reactions were mild to moderate in intensity. No evidence of a dose-relationship for the frequency or severity of adverse reactions was observed. The adverse reaction profile in elderly subjects was consistent with younger subjects.

List of adverse reactions

Table 1 shows adverse reactions that occurred in at least 2% of subjects treated with daridorexant and more frequently (≥ 1%) than in subjects who received placebo in Study 1 and Study 2.
The frequency of adverse reactions is defined using the following MedDRA frequency convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

Table 1: Adverse reactions

System organ class	Adverse reaction	Frequency
Psychiatric disorders	Hallucinations	Uncommon
Nervous system disorders	Headache	Common
	Somnolence	Common
	Dizziness	Common
	Sleep paralysis	Uncommon

General disorders and administration site conditions	Fatigue	Common
Gastro-intestinal disorders	Nausea	Common

The adverse reactions reported during long-term treatment up to 1 year were consistent with those observed during the first 3 months of treatment.

Description of selected adverse reactions in the 3-month studies

Sleep paralysis was reported in 0.5% and 0.3% subjects receiving daridorexant 25 mg and 50 mg, respectively, compared to no reports for placebo. Hallucinations were reported in 0.6% subjects receiving daridorexant 25 mg compared to no cases with daridorexant 50 mg or placebo.

Withdrawal symptoms

In controlled efficacy and safety studies, withdrawal effects were assessed by the Tyrer Benzodiazepine Withdrawal Symptom Questionnaire following discontinuation of 10 mg, 25 mg, and 50 mg daridorexant, and by adverse event reporting during a single-blind placebo run-out period. There was no evidence of withdrawal symptoms upon drug discontinuation in clinical trials with daridorexant in subjects with insomnia. This suggests that daridorexant does not produce physical dependence. With regard to investigations for withdrawal symptoms and rebound insomnia, see also “Warnings and precautions”.
Reporting suspected adverse reactions after authorization of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

There is limited clinical experience with daridorexant overdose. In clinical pharmacology studies, healthy subjects were administered single doses of up to 200 mg daridorexant (4 times the recommended dose). At supra-therapeutic doses, adverse reactions of somnolence, muscular weakness, disturbance in attention, fatigue, headache, and constipation were observed.
There is no specific antidote to an overdose of daridorexant. In the event of an overdose, general symptomatic and supportive medical care, along with immediate gastric lavage where appropriate, should be provided and patients should be carefully monitored. Dialysis is unlikely to be effective as daridorexant is highly protein bound.

Properties/Effects

ATC code

Pharmacotherapeutic group: Psycholeptics, Orexin receptor antagonists, ATC code: N05CJ03.

Mechanism of action

Daridorexant is a specific and potent dual orexin receptor antagonist, acting on both orexin 1 and orexin 2 receptors and equipotent on both. The orexin neuropeptides (orexin A and orexin B) act on orexin receptors to promote wakefulness. Daridorexant antagonises the activation of orexin receptors by the orexin neuropeptides and consequently decreases the wake drive, allowing sleep to occur.

Pharmacodynamics

Proportion of sleep stages

In subjects with insomnia, daridorexant increases both non-REM and REM sleep without altering proportion of sleep stages, as assessed by polysomnography.

Cardiac electrophysiology

200 mg daridorexant, 4 times the recommended dose, did not prolong the QTc interval.

Clinical efficacy

The efficacy of daridorexant was evaluated in two multicentre, randomised, double-blind, placebo-controlled, parallel-group, confirmatory Phase 3 studies, Study 1 and Study 2, which were identical in design.

A total of 1854 subjects with DSM-5® insomnia were randomised to receive daridorexant or placebo once daily, in the evening, for 3 months. Study 1 randomised 930 subjects to daridorexant 50 mg (N = 310), 25 mg (N = 310), or placebo (N = 310). Study 2 randomised 924 subjects to daridorexant 25 mg (N = 309), 10 mg (N = 307), or placebo (N = 308).

At the end of the 3-month treatment period, both confirmatory studies included a 7-day placebo run-out period, after which subjects could enter a 9-month double-blind, placebo-controlled extension study (Study 3). A total of 576 subjects were treated with daridorexant for at least 6 months of cumulative treatment, including 331 treated for at least 12 months.

In Study 1, subjects had a mean age of 55.4 years (range 18 to 88 years), with 39.1% of subjects ≥ 65 years of age, including 5.8% ≥ 75 years of age. The majority were female (67.1%) and White (90.2%).

In Study 2, subjects had a mean age of 56.7 years (range 19 to 85 years), with 39.3% of subjects ≥ 65 years of age, including 6.1% ≥ 75 years of age. The majority were female (69.0%) and White (87.8).

Primary efficacy endpoints for both studies were the change from baseline to Month 1 and Month 3 in Latency to Persistent Sleep (LPS) and Wake After Sleep Onset (WASO), measured objectively by polysomnography in a sleep laboratory. LPS is a measure of sleep induction and WASO is a measure of sleep maintenance.

Secondary endpoints included in the statistical testing hierarchy with Type 1 error control were patient-reported Total Sleep Time (sTST), evaluated every morning at home using a validated Sleep Diary Questionnaire (SDQ), and patient-reported daytime functioning, assessed using the sleepiness domain of the validated Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ), every evening at home. The IDSIQ total score, Alert/cognition, and Mood domain scores were also evaluated to complete the assessment of daytime functioning.

Effect of daridorexant on sleep and daytime functioning

In Study 1, doses of 25 and 50 mg daridorexant showed a statistically significant improvement vs placebo on objective (LPS, WASO) and subjective (sTST) sleep variables, at Month 1 and Month 3. The dose of 50 mg daridorexant also showed a statistically significant improvement in the IDSIQ sleepiness domain score. The magnitude of effect was highest with 50 mg across all endpoints (Table 2).

In Study 2, daridorexant 25 mg showed a statistically significant improvement vs placebo on objective (WASO) and subjective (sTST) sleep variables at Month 1 and Month 3 (Table 3).

The efficacy of daridorexant was similar across subgroups based on age, sex, race and region.

Table 2: Efficacy on sleep variables and daytime functioning – Study 1

		50 mg N = 310	**25 mg N = 310**	**Placebo N = 310**
WASO (wake after sleep onset, min): sleep maintenance, assessed objectively by PSG				
Baseline	Mean (SD)	95 (38)	98 (39)	103 (41)
Month 1	Mean (SD)	65 (35)	77 (42)	92 (42)
	Change from baseline LSM (95% CL)	-29 [-33, -25]	-18 [-22, -15]	-6 [-10, -2]
	Difference to placebo LSM (95% CL)	-23 [-28, -18]	-12 [-17, -7]	
Month 3	Mean (SD)	65 (39)	73 (40)	87 (43)
	Change from baseline LSM (95% CL)	-29 [-33, -25]	-23 [-27, -19]	-11 [-15, -7]
	Difference to placebo LSM (95% CL)	-18 [-24, -13]	-12 [-17, -6]	
LPS (latency to persistent sleep, min): sleep onset, assessed objectively by PSG				
Baseline	Mean (SD)	64 (37)	67 (39)	67 (40)
Month 1	Mean (SD)	34 (27)	38 (32)	46 (36)
	Change from baseline LSM (95% CL)	-31 [-35, -28]	-28 [-32, -25]	-20 [-23, -17]
	Difference to placebo LSM (95% CL)	-11 [-16, -7]	-8 [-13, -4]	
Month 3	Mean (SD)	30 (23)	36 (34)	43 (34)
	Change from baseline LSM (95% CL)	-35 [-38, -31]	-31 [-34, -27]	-23 [-26, -20]
	Difference to placebo LSM (95% CL)	-12 [-16, -7]	-8 [-12, -3]	

sTST (subjective total sleep time, min): patient-reported				
Baseline	Mean (SD)	313 (58)	310 (60)	316 (53)
Month 1	Mean (SD)	358 (74)	345 (66)	338 (65)
	Change from baseline LSM (95% CL)	44 [38, 49]	34 [29, 40]	22 [16, 27]
	Difference to placebo LSM (95% CL)	22 [14, 30]	13 [5, 20]	
Month 3	Mean (SD)	372 (79)	358 (72)	354 (73)
	Change from baseline LSM (95% CL)	58 [51, 64]	48 [41, 54]	38 [31, 44]
	Difference to placebo LSM (95% CL)	20 [11, 29]	10 [1, 19]	
IDSIQ sleepiness domain score (daytime functioning): patient-reported				
Baseline	Mean (SD)	22.5 (7.2)	22.1 (6.9)	22.3 (6.9)
Month 1	Mean (SD)	18.6 (7.8)	19.4 (7.1)	20.3 (6.9)
	Change from baseline LSM (95% CL)	-3.8 [-4.3, -3.2]	-2.8 [-3.3, -2.2]	-2.0 [-2.6, -1.5]
	Difference to placebo LSM (95% CL)	-1.8 [-2.5, -1.0]	-0.8 [-1.5, 0.0]	
Month 3	Mean (SD)	16.5 (8.1)	17.3 (7.6)	18.5 (7.8)
	Change from baseline LSM (95% CL)	-5.7 [-6.4, -5.0]	-4.8 [-5.5, -4.1]	-3.8 [-4.5, -3.1]
	Difference to placebo LSM (95% CL)	-1.9 [-2.9, -0.9]	-1.0 [-2.0, 0.0]	

CL = confidence limits; IDSIQ = Insomnia Daytime Symptoms and Impacts Questionnaire; LSM = least squares mean; PSG = polysomnography; SD = standard deviation.

Table 3: Efficacy on sleep variables and daytime functioning – Study 2

		25 mg N = 309	**Placebo N = 308**
WASO (wake after sleep onset, min): sleep maintenance, assessed objectively by PSG			
Baseline	Mean (SD)	106 (49)	108 (49)
Month 1	Mean (SD)	80 (44)	93 (50)
	Change from baseline LSM (95% CL)	-24 [-28, -20]	-13 [-17, -8]
	Difference to placebo LSM (95% CL)	-12 [-18, -6]	
Month 3	Mean (SD)	80 (49)	91 (47)
	Change from baseline LSM (95% CL)	-24 [-29, -19]	-14 [-19, -9]
	Difference to placebo LSM (95% CL)	-10 [-17, -4]	
LPS (latency to persistent sleep, min): sleep onset, assessed objectively by PSG			
Baseline	Mean (SD)	69 (41)	72 (46)
Month 1	Mean (SD)	42 (39)	50 (40)
	Change from baseline LSM (95% CL)	-26 [-31, -22]	-20 [-24, -16]

	Difference to placebo LSM (95% CL)	-6 [-12, -1]	
Month 3	Mean (SD)	39 (37)	49 (46)
	Change from baseline LSM (95% CL)	-29 [-33, -24]	-20 [-24, -15]
	Difference to placebo LSM (95% CL)	-9 [-15, -3]	
sTST (subjective total sleep time, min): patient-reported			
Baseline	Mean (SD)	308 (53)	308 (52)
Month 1	Mean (SD)	353 (67)	336 (63)
	Change from baseline LSM (95% CL)	44 [38, 49]	28 [22, 33]
	Difference to placebo LSM (95% CL)	16 [8, 24]	
Month 3	Mean (SD)	365 (70)	347 (65)
	Change from baseline LSM (95% CL)	56 [50, 63]	37 [31, 43]
	Difference to placebo LSM (95% CL)	19 [10, 28]	
IDSIQ sleepiness domain score (daytime functioning): patient-reported			
Baseline	Mean (SD)	22.2 (6.2)	22.6 (5.8)
Month 1	Mean (SD)	18.7 (6.5)	19.8 (6.3)
	Change from baseline LSM (95% CL)	-3,5 [-4.1, -2.9]	-2.8 [-3.3, -2.2]
	Difference to placebo LSM (95% CL)	-0.8 [-1,6, 0.1]	
Month 3	Mean (SD)	17.0 (7.0)	18.4 (6.6)
	Change from baseline LSM (95% CL)	-5.3 [-6.0, -4.6]	-4.0 [-4.7, -3.3]
	Difference to placebo LSM (95% CL)	-1.3 [-2.2, -0.3]	

CL = confidence limits; IDSIQ = Insomnia Daytime Symptoms and Impacts Questionnaire; LSM = least squares mean; PSG = polysomnography; SD = standard deviation.

The effects of daridorexant on sleep variables were observed early in treatment and were maintained over time. The change from baseline in sTST was observed within the first week and continued to improve over time.

Over the course of the trials, sleep quality, assessed by subjects every morning using a visual analogue scale, was improved across all treatment groups, in a dose-dependent manner.

Rebound insomnia

The potential for rebound insomnia was assessed during the placebo run-out period after 3 months of treatment with daridorexant in Study 1 and Study 2, looking at the change from baseline to the run-out period in LPS, WASO and sTST. No sign of rebound insomnia was observed upon treatment discontinuation.

With regard to investigations for withdrawal symptoms and rebound insomnia, see also “Warnings and precautions”.

Paediatrics

The European Medicines Agency has deferred the obligation to submit the results of studies with daridorexant in one or more subsets of the paediatric population in insomnia.

Pharmacokinetics

Absorption

Daridorexant (25 mg and 50 mg o.d.) is rapidly absorbed following oral administration and reaches peak plasma concentrations within 1–2 h. At an oral dose of 100 mg, daridorexant has an absolute bioavailability of 62%. Across studies, exposure parameters C_{max} and $AUC_{0\text{-}24h}$ at 50 mg are approximately 1100 ng/mL and 6700 ng/mL·h, respectively.
Daridorexant plasma exposure is dose proportional between 25 mg and 50 mg.

Effect of food
In healthy subjects, food did not affect total exposure. The maximum concentration of 50 mg daridorexant was delayed by 1.3 h and C_{max} decreased by 16% following administration of a high-fat and high-calorie meal.

Distribution

Daridorexant has a volume of distribution of 31 L. Daridorexant is extensively bound (99.7%) to plasma proteins. The blood to plasma ratio is 0.64.

Metabolism

Daridorexant undergoes extensive metabolism and is primarily metabolised by CYP3A4 (89%). Other CYP enzymes are not of clinical relevance and individually contribute to less than 3% of metabolic clearance. In human plasma, parent daridorexant accounted for 20.9% of total drug-related material, while the 3 major metabolites accounted for 28.9% (M3), 12.7% (M1) and 9.0% (M10), respectively. None of the major human metabolites M1, M3 and M10 contribute to the pharmacological effect of the medicinal product.

Elimination

The primary route of excretion is via faeces (approximately 57%), followed by urine (approximately 28%). Only traces of parent drug were found in urine and faeces.
The clearance was 5 L/h and the terminal half-life of daridorexant is approximately 8 hours.

The PK profile of daridorexant following multiple-dose administration showed PK parameters similar to those observed after single-dose administration. No accumulation was observed.

Kinetics in specific patient groups

Based on a population-pharmacokinetic analysis, no clinically significant differences in the PK of daridorexant were detected based on age (mean, median and range), sex (female, male), race (White, Black or African American, Japanese, others), or body size (weight, body mass index).

Hepatic impairment

Following administration of a single dose of 25 mg daridorexant, subjects with mild hepatic impairment (Child-Pugh score 5–6) had a similar exposure to unbound daridorexant compared to healthy subjects. In subjects with moderate hepatic impairment (Child-Pugh score 7–9), exposure to unbound daridorexant (AUC) and $t_{1/2}$ increased by 1.6 times and 2.1 times, respectively, compared to healthy subjects.
Based on these results, a dose adjustment is recommended in patients with moderate hepatic impairment (see Section Dosage).
In patients with severe hepatic impairment (Child-Pugh score ≥ 10), daridorexant has not been studied and is not recommended.

Renal impairment

Following administration of a single dose of 25 mg, the PK parameters of daridorexant were similar in subjects with severe renal impairment compared to healthy subjects.
Based on these results, QUVIVIQ can be administered to patients with any degree of renal function impairment without the need for dose adjustment.

Preclinical data

Nonclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity, carcinogenicity and reproductive toxicity. No effects on reproductive variables including teratogenicity and juvenile development have been identified for daridorexant and no drug abuse liability has been demonstrated.

Repeated dose toxicity

No undesirable effects were observed in repeated dose toxicity studies in rats and dogs at exposures that are 61 times and 14 times, respectively, the human exposure at the maximum recommended dose of 50 mg/day, based on the free plasma exposure ($AUC_{0–24h\ unbound}$).
In dogs under positive stimulation at play, episodes of sudden muscle weakness, reminiscent of cataplexy, were observed from Week 7 onwards and did not occur after treatment cessation. An overall

NOEL of 20 mg/kg/day was established at exposures, based on the free plasma exposure ($AUC_{0\text{-}24\ unbound}$) that are 31 times (females) and 54 times (males) the human exposure at 50 mg/day.

Toxicity tests with juvenile animals

Daridorexant showed no effect on juvenile development in rats. Juvenile rats were treated with daridorexant doses up to 450 mg/kg/day, once daily administration by oral gavage from weaning (PND21) to adulthood (PND84), supporting clinical trials in children from 2 years of age and older. No relevant effects were observed on development, behaviour, learning, memory, or histopathology. A safety margin of 73 was established to the human exposure at 50 mg, based on the free plasma exposure ($AUC_{0–24h\ unbound}$).

Other data

Daridorexant showed no signs indicative of abuse potential or physical dependence in rats. Daridorexant at an oral dose of 0 (vehicle), 20 and 200 mg/kg/day did not induce any notable changes in physiological, neurobehavioral, or locomotor activity parameters associated with the development of a withdrawal syndrome after 4 weeks of treatment. Daridorexant did not lead to self-administration in rats with a previous history of cocaine self-administration, and there was no similarity between the discriminative effects of zolpidem and the effects induced by daridorexant at any of the doses tested. Safety margins of 18–27 were established to the human exposure at 50 mg, based on the free plasma exposure ($C_{max\ unbound}$).

Other information

Incompatibilities

Not applicable.

Shelf life

The drug may only be used up to the date marked “EXP” on the pack.

Special precautions for storage

Do not store above 30°C.
Store drug out of reach of children.

Authorisation Number

68481

Packs

Packs of 10 or 30 tablets of 25 mg [B].

Packs of 10 or 30 tablets of 50 mg [B].

Marketing authorization holder

IDORSIA PHARMACEUTICALS LTD
4123 ALLSCHWIL
SWITZERLAND

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