SUMMARY OF PRODUCT CHARACTERISTICS

▼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 adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

QUVIVIQ 25 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains daridorexant hydrochloride equivalent to 25 mg of daridorexant.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Light purple arc-triangle shaped film-coated tablets, debossed with ‘25’ on one side, and ‘i’ on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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.

4.2 Posology and method of administration

Posology

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 sections 4.4 and 4.5).

The maximum daily dose is 50 mg.

The treatment duration should be as short as possible. The appropriateness of continued treatment should be assessed within 3 months and periodically thereafter. Clinical data are available for up to 12 months of continuous treatment.

Treatment can be stopped without down-titration.

Missed dose

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

Hepatic impairment

In patients with mild hepatic impairment, no dose adjustment is required. In patients with moderate hepatic impairment, the recommended dose is one tablet of 25 mg once per night (see section 5.2). In patients with severe hepatic impairment, daridorexant has not been studied and is not recommended (see section 4.4).

Renal impairment

In patients with renal impairment (including severe), no dose adjustment is required (see section 5.2).

Co-administration with moderate CYP3A4 inhibitors

The recommended dose when used with moderate CYP3A4 inhibitors is one tablet of 25 mg once per night (see section 4.5).

The consumption of grapefruit or grapefruit juice in the evening should be avoided.

Co-administration with central nervous system (CNS) depressants

In the case of co-administration with CNS-depressant medicinal products, dose adjustments of QUVIVIQ and/or the other medicinal products may be required, based on clinical evaluation, due to potentially additive effects (see sections 4.4 and 4.5).

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.

Paediatric population

The safety and efficacy of daridorexant in paediatric patients have not yet been established. No data are available.

Method of administration

For oral use.

QUVIVIQ can be taken with or without food. However, taking QUVIVIQ soon after a large meal may reduce the effect on sleep onset (see section 5.2).

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Narcolepsy.
- Concomitant use with strong CYP3A4 inhibitors (see section 4.5).

4.4 Special warnings and precautions for use

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, especially in the first few days of treatment (see section 4.7).

Caution should be exercised when prescribing QUVIVIQ concomitantly with CNS-depressant medicinal products due to potentially additive effects, and a dose adjustment of either QUVIVIQ or the concomitant CNS depressants should be considered.

Patients should be cautioned about drinking alcohol during treatment with QUVIVIQ (see section 4.5).

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, mainly during the first weeks of treatment (see section 4.8).

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. Should such events occur, patients need to be further evaluated and, depending on the nature and severity of the events, discontinuation of treatment should be considered.

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 studies, in subjects with pre-existing psychiatric conditions and/or stressful living conditions, across all treatment groups, including placebo. Suicidal tendencies may be present in patients with depression and protective measures may be required.

Patients with psychiatric co-morbidities

QUVIVIQ should be administered with caution in patients with psychiatric co-morbidities since efficacy and safety data in this patient population are limited.

Patients with compromised respiratory function

Daridorexant did not increase the frequency of apnoea/hypopnoea events or cause oxygen desaturation in patients with mild to moderate (5 to < 30 events per hour of sleep) or severe (≥ 30 events per hour of sleep) obstructive sleep apnoea (OSA). Nor did it cause oxygen desaturation in patients with moderate chronic obstructive pulmonary disease (COPD). Daridorexant has not been studied in patients with severe COPD (FEV_1 < 40% of predicted).

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

Potential for abuse and dependence

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.

In an abuse liability study of daridorexant (50, 100 and 150 mg) conducted in non-insomniac recreational drug users (n = 72), daridorexant (100 and 150 mg) produced similar “drug liking” ratings as zolpidem (30 mg). 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.

Hepatic impairment

Use is not recommended in patients with severe hepatic impairment (see sections 4.2 and 5.2).

Excipients

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medicinal products 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 4.3).

The consumption of grapefruit or grapefruit juice in the evening should be avoided.

CYP3A4 inducers
In healthy subjects, co-administration with efavirenz (600 mg once daily), 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 daridorexant, 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 39% while AUC remained unchanged.

No dose adjustment is required when QUVIVIQ is used concomitantly with treatments that reduce gastric acidity.

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 medicinal products

Substrates of CYP3A4
In a clinical study conducted in healthy subjects receiving daridorexant and midazolam, a sensitive CYP3A4 substrate, daridorexant at a dose of 25 mg did not affect the PK of midazolam, 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, daridorexant 50 mg administered for 7 days did not induce CYP3A4, therefore contraceptives can be co-administered with QUVIVIQ.

Substrates of CYP2C9
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.

Substrates of BCRP or P-gp transporters
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.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, 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 section 5.3).

Consequently, QUVIVIQ should be used during pregnancy only if the clinical condition of the pregnant woman requires treatment with daridorexant.

Breast-feeding

Available data from a lactation study in 10 healthy lactating women receiving 50 mg daridorexant indicates that the presence of daridorexant in breast milk is low, with a fraction of the maternal dose of daridorexant excreted into breast milk of 0.02%.

A risk of excessive somnolence to the breastfed infant cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from QUVIVIQ therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There are no data concerning the effect of exposure to daridorexant on human fertility. Animal studies indicate no impact on male or female fertility (see section 5.3).

4.7 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, 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 non-

insomniac, healthy subjects aged from 50 to 79 years. Testing was conducted after 1 night (initial dosing) and after 4 consecutive nights of treatment with daridorexant 50 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 the Lateral Position (SDLP). 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 4.4). In order to minimise this risk, a period of approximately 9 hours is recommended between taking QUVIVIQ and driving or using machines.

4.8 Undesirable effects

Summary of safety profile

The most frequently reported adverse reactions were headache and somnolence.

The majority of 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.

Tabulated list of adverse reactions

Table 1 shows adverse reactions that occurred in Study 1 and Study 2 or in post-marketing experience.

The frequency of adverse reactions is defined using the following 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). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

The safety of daridorexant was evaluated in three placebo-controlled Phase 3 clinical studies. 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.

Table 1: Adverse reactions

System organ class	Adverse reaction	Frequency

Immune system disorders	Hypersensitivity (including rash, urticaria)	Uncommon
Psychiatric disorders	Hallucination	Uncommon
	Abnormal dreams, nightmares	Uncommon
	Somnambulism	Uncommon
Nervous system disorders	Headache	Common
	Somnolence	Common
	Dizziness	Common
	Sleep paralysis	Uncommon
Gastrointestinal disorders	Nausea	Common
General disorders and administration site conditions	Fatigue	Common

Description of selected adverse reactions

Somnolence
Somnolence was reported in 3% and 2% of subjects treated with daridorexant 25 mg and 50 mg, respectively, compared to 2% of subjects on placebo.

Sleep paralysis and hallucinations
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. Hypnagogic and hypnopompic hallucinations were reported in 0.6% subjects receiving daridorexant 25 mg compared to no cases with daridorexant 50 mg or placebo. Sleep paralysis and hallucinations occur mainly during the first weeks of treatment.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 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 should be provided and patients should be carefully monitored. Dialysis is unlikely to be effective as daridorexant is highly protein-bound.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psycholeptics, orexin receptor antagonists, ATC code: N05CJ03

Mechanism of action

Daridorexant is a 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, without altering the proportion of sleep stages (as assessed by electroencephalographic recording in rodents or polysomnography in patients with insomnia).

Clinical efficacy and safety

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

A total of 1854 subjects with insomnia disorder (dissatisfaction with sleep quantity or quality, for at least 3 months, with clinically significant distress or impairment in daytime functioning) 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 baseline, the proportion of subjects with an Insomnia Severity Index (ISI) score between 8–14, 15–21, and 22–28, was 12%, 58%, and 30%, respectively.

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 331treated 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%).

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%).

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 Sleep Diary Questionnaire (SDQ), and patient-reported daytime functioning, assessed using the sleepiness domain of the 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
Across the two studies, the efficacy of daridorexant increased with increasing dose on objective (LPS, WASO) and subjective (sTST) sleep variables as well as on daytime functioning as assessed by IDSIQ scores, both at Month 1 and Month 3.

In Study 1, the 50 mg dose showed statistically significant ($p < 0.001$) improvements compared to placebo on all primary and secondary endpoints. For the 25 mg dose, statistical significance was consistently achieved on WASO and sTST across both studies, and on LPS in Study 1. The 10 mg dose was not effective.

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	-35	-31	-23

	LSM (95% CL)	[-38, -31]	[-34, -27]	[-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.

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. At the recommended dose of 50 mg, for all three endpoints, the mean values at run-out were improved compared to baseline (–15, –3 and 43 min for LPS, WASO and sTST, respectively), indicating that no sign of rebound insomnia was observed upon treatment discontinuation.

Middle of the night safety

The effect of daridorexant on middle of the night safety was evaluated in a randomised, placebo-controlled trial in 18 healthy adult (< 65 years) and 18 healthy elderly (≥ 65 years) subjects. Postural stability measured by assessing body sway using a body sway meter approximately 5 min after awakening was assessed following a scheduled awakening 4 hours after administration of 25 or 50 mg

daridorexant. The ability to awaken in response to a sound stimulus and cognitive function (memory) were also evaluated.

In the subgroup of healthy adults (< 65 years), nighttime dosing of daridorexant 25 mg and 50 mg resulted in increased body sway, with differences in least squares mean (95% CI) of 64.8 mm (16.0, 113.7) and 97.3 mm (48.4, 146.1), respectively, as compared to placebo.

Paediatric population

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 (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Daridorexant 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%.

Daridorexant plasma exposure is dose proportional between 25 and 50 mg.

Effect of food

In healthy subjects, food did not affect total exposure. The t_{max} 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, mostly to albumin and to a lower extent to α-acid glycoprotein. The blood to plasma ratio is 0.64.

Biotransformation

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. None of the major human metabolites (M1, M3, and M10) contribute to the pharmacological effect of the medicinal product.

Daridorexant inhibits several CYP enzymes *in vitro*. The strongest inhibition was seen on CYP3A4 with a K_i of 4.6–4.8 µM (see section 4.5). 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 3 µM. Daridorexant does not induce CYP1A2.

Daridorexant inhibits various transporters *in vitro* and had the strongest inhibitory effect on BCRP with an IC_{50} of 3.0 µM (see section 4.5). Inhibition of other transporters including OATP, OAT3, OCT1, MATE-2K, MATE1, and P-gp/MDR1 was less pronounced, with IC_{50} values ranging from 8.4–71 µM.

Elimination

The primary route of excretion is via faeces (approximately 57%), followed by urine (approximately 28%). Only traces of parent compound were found in urine and faeces.

The terminal half-life of daridorexant is approximately 8 hours.

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

Pharmacokinetics in special populations

No clinically significant differences in the PK of daridorexant were detected based on age, sex, race, or body size. Limited PK data are available in patients older than 75 years.

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 half-life 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 4.2).

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, daridorexant can be administered to patients with any degree of renal function impairment without the need for dose adjustment.

5.3 Preclinical safety data

Nonclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeat-dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development. Daridorexant also showed no signs indicative of abuse potential or physical dependence.

No adverse effects were observed in repeat-dose toxicity studies in rats and dogs at exposures that are 72 times and 14 times, respectively, the human exposure at the maximum recommended dose of 50 mg/day.

In dogs under positive stimulation at play, episodes of sudden muscle weakness, reminiscent of cataplexy, were observed as exaggerated pharmacological effects of daridorexant from Week 7 onwards and did not occur after treatment cessation. An overall no-observed-effect level was established at exposures that are 45 times (females) and 78 times (males) the human exposure at 50 mg/day for the free fraction.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Mannitol (E421)

Microcrystalline cellulose (E460)

Povidone

Croscarmellose sodium

Silicon dioxide

Magnesium stearate

Film coat

Hypromellose (E464)

Microcrystalline cellulose (E460)

Glycerol

Talc (E553)

Titanium dioxide (E171)

Iron oxide red (E172)

Iron oxide black (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Polyvinyl chloride (PVC) coated with polyvinylidene chloride (PVdC) and laminated with PVC film blister sealed with an aluminium foil blister, packed in a carton box.

Pack size of 10 or 30 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Idorsia Pharmaceuticals Deutschland GmbH

Marie-Curie-Strasse 8

79539 Lörrach

Germany

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 48711/0002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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