swissmedic

Date: 31 May 2023
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

QUVIVIQ

International non-proprietary name: daridorexant as daridorexant hydrochloride

Pharmaceutical form: film-coated tablet

Dosage strength(s): 25 mg, 50 mg

Route(s) of administration: oral

Marketing authorisation holder: Idorsia Pharmaceuticals Ltd

Marketing authorisation no.: 68481

Decision and decision date: approved on 1 December 2022

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

Table of contents

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CNS	Central nervous system
CYP	Cytochrome P450
DDI	Drug-drug interaction
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
KSS	Karolinska Sleepiness Scale
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
IV	Intravenous
LoQ	List of Questions
LPS	Latency to persistent sleep
LSM	Least square mean
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
QD	Once daily
RMP	Risk management plan
SAE	Serious adverse event
SPV	Smooth pursuit velocity
SSRI	Selective Serotonin Reuptake Inhibitor
sTST	Subjective total sleep time
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
VAS	Visual analogue scale
WASO	Wake after sleep onset

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

2 Background Information on the Procedure

2.1 Applicant's Request(s)

New active substance status
The applicant requested new active substance status for daridorexant in the above-mentioned medicinal product.

2.2 Indication and dosage

2.2.1 Requested indication

QUVIVIQ is indicated for the treatment of adult patients with insomnia to improve sleep and daytime functioning.

2.2.2 Approved indication

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.

2.2.3 Requested dosage

Summary of the requested standard dosage:

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.

Patients with hepatic impairment

The recommended dose in patients with moderate hepatic impairment is one tablet of 25 mg once per night.

Co-administration with moderate CYP3A4 inhibitors

The recommended dose when used with moderate CYP3A4 inhibitors is one tablet of 25 mg once per night.

Co-administration with CNS depressants

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.

Method of administration

QUVIVIQ can be taken with or without food, however sleep onset may be delayed if taken with, or soon, after a high-fat and high-calorie meal.

2.2.4 Approved dosage

(see appendix)

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

2.3 Regulatory history (milestones)

Application	21 April 2021
Formal control completed	2 July 2021
List of Questions (LoQ)	22 November 2021
Response to LoQ	3 March 2022
Preliminary decision	25 May 2022
Response to preliminary decision	12 July 2022
Labelling corrections	19 September 2022
Response to labelling corrections	30 September 2022
Final decision	1 December 2022
Decision	approval

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

3 Medical context

Insomnia disorder (as studied according to the DSM-5 definition in the daridorexant development programme) is common and associated with impairment in daily functioning and other medical comorbidities. Key aspects of insomnia disorder are 1) the difficulty of initiating sleep, 2) the difficulty of maintaining sleep and waking too early and 3) nonrestorative sleep leading to impaired daytime functioning, despite adequate opportunity and circumstances for sleep.

The standard of care for the treatment of insomnia disorder as per clinical guidelines consists of cognitive behavioural therapy and pharmacological treatments. Several approved (and also off-label) drugs are used for the treatment of insomnia.

However, available treatment options for insomnia are limited due to safety risks like abuse potential, dependency and withdrawal effects, next-morning residual effects and the problematic long-term use (due to the lack of long-term data or the side effects). Short-acting drugs with fewer or no next-morning residual effects typically show insufficient effects on sleep maintenance.

The neuropeptides orexin A and orexin B act on orexin receptors to promote wakefulness. Orexin receptor antagonists such as daridorexant antagonise the activation of orexin receptors by both orexin peptides and consequently decrease the wake-drive.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

4 Quality aspects

4.1 Drug substance

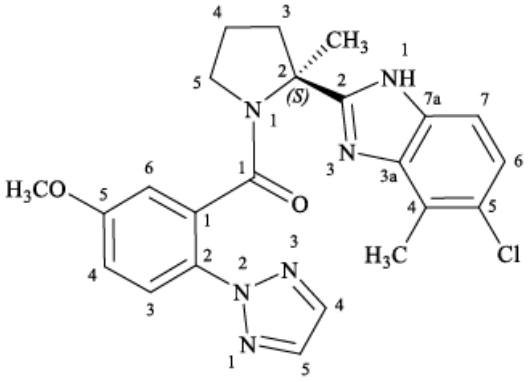
INN: Daridorexant hydrochloride

Chemical name: [(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 hydrochloride

Molecular formula: $C_{23}H_{23}ClN_6O_2 \cdot HCl$

Molecular mass: 487.38

Molecular structure:



• HCl

Physico-chemical properties: White to light yellow non-hygroscopic powder

Stereochemistry: Daridorexant HCl has one asymmetric centre and is manufactured as the S-isomer.

Polymorphism: Daridorexant HCl is manufactured in the anhydrous polymorphic form A.

Synthesis: Daridorexant hydrochloride drug substance is manufactured at one manufacturer's site by a convergent synthesis comprising three steps for each branch of the convergent process, from the introduction of the starting materials, with three isolated intermediates, followed by micronisation at a second manufacturer's site.

Specification: Appearance, colour, sulphated ash, water content, identity of daridorexant, identity of chloride, content of chloride, residual solvents, related substances, assay, enantiomeric ratio, particle size distribution, microbial quality.

Stability: Stability studies have been performed with the drug substance. No significant changes in any parameters were observed. An appropriate retest period has been set.

4.2 Drug product

Description and composition: QUVIVIQ is an immediate-release, arc-triangle shaped film-coated tablet available in 25 and 50 mg strengths, both approximately 7 mm in diameter and 4 mm in thickness. The 25 mg tablet is light purple and debossed with “25” on one face. The 50 mg tablet is light orange and debossed with “50” on one face. Tablets of both strengths are debossed with the Idorsia logo on the other face.

Pharmaceutical development: The drug substance has a pH-dependent solubility profile, with highest solubility at an acidic pH. The aim of pharmaceutical development was to produce an immediate-release tablet with rapid disintegration and a high dissolution rate.
Well known standard excipients of film-coated tablet manufacture that comply with the Ph. Eur. standards or the applicable foodstuff standards (colourants) have been selected.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

Manufacture: QUVIVIQ film-coated tablets are manufactured by a standard process that includes wet granulation, drying, sieving, blending (extra-granular phase), lubrication, tablet compression and film coating. The process was optimised by a mix of traditional development studies and principles of quality by design.

Specification: For the control of the finished product, adequate tests and acceptance criteria for release and at shelf-life are established. The specifications include the parameters appearance, colour, water content, identification tests, uniformity of dosage units (Ph. Eur.), assay (HPLC), degradation products (HPLC), dissolution (HPLC) and microbial quality. The corresponding analytical test procedures have been adequately validated.

Container Closure System: QUVIVIQ film-coated tablets are packaged in polyvinyl chloride (PVC) / polyvinylidene dichloride (PVdC) / PVC film with push-through aluminium foil blisters.

Stability: Stability data have been generated in the packaging material for commercial use and following the relevant ICH guidelines for three batches of each strength. Based on these studies a shelf life of 36 months was established for the film-coated tablets. The storage recommendation is “Do not store above 30°C”.

4.3 Quality conclusions

Satisfactory and consistent quality of drug substance and drug product has been demonstrated.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

5 Nonclinical aspects

5.1 Pharmacology

In vitro, studies showed that daridorexant is a selective orexin receptor antagonist acting on both orexin 1 (OX1) and orexin 2 (OX2) receptors in rats, dogs, and humans, with no significant differences in potency or between species, and antagonistic potency (apparent K_b) values ranging from 0.33 to 1.7 nM.

In cell-based calcium mobilisation assays, the on-target residence times were in the ranges of 8 to 46 minutes (OX1) and 4 to 87 minutes (OX2). The major metabolites identified in humans, M1 (ACT-776537), M3 (ACT-776063), and M10 (ACT-1016-3307), have been demonstrated to be pharmacologically inactive.

In vivo, the effectiveness of sleep induction by daridorexant was demonstrated following administration of single oral doses of up to 300 mg/kg to rats and up to 90 mg to dogs (equivalent to 5.5-7.1 mg/kg). General sleep architecture was not altered, and both rats and dogs behaved normally after being woken up from a daridorexant-induced sleep.

In a secondary pharmacodynamic *in vitro* screening, potential daridorexant-related off-target activity was observed for the dopamine transporter (52%) and for phosphodiesterase PDE4 (81%). In follow-up functional assays, the IC_{50} values determined were at least 2054-fold higher than the clinical exposure at the recommended dose of 50 mg/kg daily. The applicant did not identify any off-target activity for the metabolites M1, M3, or M10 at a clinically relevant concentration. *In vivo*, daridorexant-treated rats showed no similarity to zolpidem treatment, suggesting that daridorexant does not bind and act via GABA receptors.

Daridorexant was evaluated in a core battery of *in vitro* and *in vivo* studies to assess effects on cardiovascular, respiratory, and central nervous system (CNS) function according to ICH S7A/B. At clinically relevant concentrations and exposures, daridorexant did not raise any safety concerns.

5.2 Pharmacokinetics

Pharmacokinetics of daridorexant was studied in rats and dogs. Oral absorption was rapid in both species, with peak plasma concentrations being reached within 1 to 2 hours after dosing. Oral bioavailability was in the range of 10-30% in rats and 31-58% in dogs. Systemic plasma clearance was moderate in both species with gender differences in rats (clearance higher in males). Elimination half-lives were 0.5-2.1 hours in rats and 2.5-4.1 hours in dogs, i.e. shorter than in humans ($t_{½}$ ≈ 8 hours). In humans, daridorexant is also rapidly absorbed after oral administration (T_{max} 1-2 hours), and bioavailability was 62%, which is comparable to results observed in dogs. Following repeated daily dosing, exposure to daridorexant generally increased in a more than proportional manner in rats and proportionally to dose in dogs.

In vitro plasma protein binding of daridorexant and its major metabolites was higher in humans (99.7%) than in nonclinical species (>97%).

In rats, ^{14}C-daridorexant-related radioactivity absorption was rapid (i.e. tissue T_{max} 0.5 hours post-dose) and the radioactivity was widely distributed into most tissues, crossed the blood brain barrier, and was excreted into milk. Studies with pigmented rats indicate no binding to melanin. The presence of elevated levels of radioactivity up to 72 hours post-dose in the gastrointestinal tract and bile ducts suggested that daridorexant was primarily eliminated by metabolism via the biliary/faecal route, similar to the route of elimination in humans.

The *in vitro* metabolism of daridorexant was investigated in liver microsomes and hepatocytes of mice, rats, rabbits, dogs, monkeys, and humans. Metabolism in liver microsomes of nonclinical species was faster than in human liver microsomes. There was no gender difference in the nature of metabolic products, but metabolism was slower in female rats than in males. Transformation in hepatocytes was significant and greater than in microsomes. No unique metabolites were identified in human hepatocytes. Metabolism was mainly driven by CYP3A4, which was identified as the main enzyme responsible for daridorexant metabolism (89% of metabolic clearance). *In vivo*, daridorexant was extensively metabolised. Unchanged daridorexant was the major component in plasma samples

in rats. The major human plasma metabolites M1, M3, and M10 were also identified in rats and dogs, and sufficient exposure was demonstrated in the pivotal repeat-dose toxicity and reproductive studies.

5.3 Toxicology

The toxicological profile of daridorexant was evaluated in mice, rats, rabbits, and dogs. The selection of rat and dog as species for toxicological assessment is considered appropriate as metabolism of daridorexant, pharmacodynamic effects (i.e. sleep induction), and pharmacokinetic profile are comparable in both species and humans. The route of administration (i.e. oral) and frequency of dosing in the nonclinical studies are consistent with the proposed clinical setting (once daily dosing).

Pivotal repeat-dose oral toxicity studies were conducted up to 26 weeks in rats at doses of 50, 150 or 450 mg/kg/day and 39 weeks in dogs at doses of 0, 10, 30 or 100 mg/kg/day.

Pharmacology-related clinical signs including catalepsy, lying down, loss of balance, unsteady gait, clumsy movements, inability to stand and/or immobility were observed in rats at ≥ 50 mg/kg/day and dogs at ≥ 30 mg/kg/day. These clinical signs were considered as signs of exaggerated pharmacology in rats and adverse in dogs due to their severity. There were no daridorexant-related clinical signs in dogs at 10 mg/kg/day. The clinical signs were no longer observed during the recovery period, and microscopic examination of the brain did not reveal any treatment-related anomalies. Since the exposure at 10 mg/kg/day was at least several times higher (> 14-fold) than the exposure in patients at the clinical dose, the risk is considered low.

The main target organs of toxicity were liver, thyroid gland, and kidneys in rats, and liver and gallbladder in dogs. Daridorexant-related centrilobular hepatocellular hypertrophy and follicular cell hypertrophy in the thyroid glands in rats were associated with clinical pathology changes and organ weight changes. The kidney findings observed in female rats at the high dose were consistent with early stages of chronic progressive nephropathy, which is not considered of clinical relevance. In dogs, liver weight increase was consistent with homogeneous enlargement of hepatocytes, which was considered secondary to drug-metabolising enzyme induction. The luminal secretory material in the gallbladder was considered a functional change related to the excretion of daridorexant. All findings were reversible or showed a tendency to reversibility following the 8-week recovery period. The findings noted in the target organs of toxicity in rats and dogs are considered non-adverse with no clinical relevance and of low risk. The safety margins at the NOAELs for systemic toxicity in the chronic toxicity studies are substantial in rats (61-fold, 26-week study) and acceptable in dogs (14-fold, 39-week study).

Daridorexant was negative in *in vitro* and *in vivo* genotoxic assays conducted according to ICH S2 (R1).

Daridorexant was not carcinogenic in rats or transgenic mice at doses up to 150 mg/kg/day and 1000 mg/kg/day, and was associated with exposure multiples vs. clinical AUC at the recommended dose of 50 mg/day of ≥ 25-fold in rats and ≥ 3-fold in mice.

In the studies on fertility, embryofoetal development, and pre-/post-natal development, no adverse effects were observed up to the highest doses, associated with exposures of ≥ 46-fold the clinical AUC at the recommended dose of 50 mg/day. This is adequately reflected in the information for healthcare professionals.

Although the current indication is for adult patients, a juvenile animal toxicity study was conducted in accordance with the EMEA PIP in rats dosed orally at 0, 50, 150 and 450 mg/kg/day to support development in paediatric patients from 2 years of age. There was no evidence that juvenile rats were more sensitive to daridorexant compared to adults.

Daridorexant was not phototoxic in the *in vitro* 3T3 neutral red uptake test.

Based on animal studies, daridorexant did not reveal any signs indicative of physical dependence or drug abuse potential.

The Nonclinical Safety Specifications in the RMP adequately address the nonclinical findings and their relevance for clinical use.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

Impurities are controlled according to ICH Q3A/B and ICH M7. There are no concerns about the excipients.

Based on the ERA, daridorexant does not represent a risk for the environment.

5.4 Nonclinical conclusions

In conclusion, the nonclinical documentation is sufficient to support the approval of QUVIVIQ (daridorexant) in the proposed indication. The pharmacodynamic studies and the safety programme do not suggest any particular adverse effects in patients. All nonclinical data relevant to safety are mentioned in the information for healthcare professionals. From the nonclinical perspective, approval may be granted in the proposed indication.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

6 Clinical and clinical pharmacology aspects

6.1 Clinical pharmacology

Biopharmaceutical Development

Throughout the entire clinical program, three different formulations of daridorexant including a soft and hard gelatin capsule as well as film-coated tablet have been developed and used. The commercial tablets are identical to the clinical tablets utilised in Phase 3, apart from the composition of the film-coating for blinding reasons. The final to-be-marketed drug product is supplied as 50 mg and 25 mg immediate-release film-coated tablets.

The impact of food on the PK of daridorexant was investigated in two biopharmaceutical studies. Following the administration of a 25 mg hard gelatin capsule, t_{max} was delayed by 1.88 h and C_{max} was decreased by 24.2%, whereas AUC was unaffected when co-administered with a high-fat, high-calorie breakfast. In line with these findings, t_{max} was delayed by 1.28 h and C_{max} was decreased by 15.6%, whereas AUC was unaffected following the administration of a 50 mg Phase 3/commercial tablet under fed conditions. In the context of the population PK analysis, it was shown that C_{max} was 36% lower under fed conditions, and t_{max} was more than twice as long. These findings indicate that the overall exposures remained unchanged, but the sleep-promoting effect could be delayed when administered with food. The food effect when daridorexant is taken simultaneously with high-fat, high-calorie food is an extreme-case scenario unlikely to occur in clinical practice. Therefore, the dosing recommendation is to take the tablet irrespective of food, which was also applied in the Phase 3 studies.

Since the solubility of daridorexant was shown to be pH-dependent, the impact on the PK when co-administered with an H2-receptor antagonist was investigated. When co-administered with famotidine, C_{max} of 50 mg daridorexant was decreased by 39% and t_{max} was delayed by 0.5 h, whereas AUC was unaffected. No dose adjustment is required.

ADME

The pharmacokinetics of daridorexant in healthy subjects following single (5 mg to 200 mg) and multiple doses (10 mg and 75 mg) was evaluated in a battery of biopharmaceutical and phase 1 studies. Sparse pharmacokinetic samples were collected in the phase 2 and 3 studies and contributed to the population PK analyses.

Absorption

After a single administration of the proposed dose of 50 mg daridorexant in healthy subjects, the peak plasma concentrations of 1115 ng/mL were reached after approximately 1 h, which resulted in AUC_{0-24} values of 6715 ng*h/mL. Using an IV 14C-labelled microtracer, the absolute bioavailability following the administration of 100 mg daridorexant was 62%.

Following 5 QD doses of the proposed dose of 50 mg daridorexant in healthy subjects, C_{max} and AUC_{0-24} at steady state were 1006 ng/mL and 6306 ng*h/mL, respectively.

Steady state appears to be reached within 2 to 3 days, and only a small extent of accumulation was observed. Based on the next-morning concentrations in the Phase 3 studies, no accumulation is expected up to 3 months.

Daridorexant exposures increased dose-proportionally between the approved doses of 25 mg and 50 mg.

Distribution

Based on ex vivo measurement, protein binding following the administration of 25 mg and 200 mg daridorexant was determined to be >99%. A mean blood/plasma ratio for total radioactivity of 0.64 suggests rather low binding to red blood cells.

Following the IV administration of a ^{14}C-labelled microtracer, the Vss of daridorexant was 31 L.

Metabolism and Elimination

In vitro human CYP phenotyping studies showed that daridorexant was metabolised by CYP3A4 (fm = 0.89) with minor contributions from CYP2C19, CYP2D6 and CYP2C9, indicating that CYP3A4 is

the primary clearance route. Daridorexant was excreted via faeces and urine accounting for 57% and 28%, respectively, of the total radioactivity. The predominant circulating entity was the metabolite M3 (28.9%), followed by parent drug (20.9%), M1 (12.7%), and M10 (9%). All other metabolites accounted for <10% of the total radioactivity in plasma. Only traces of parent drug were measured in excreta suggesting that daridorexant is primarily eliminated by metabolism.

Following the IV administration of a ^{14}C-labelled microtracer, the clearance of daridorexant was 5 L/h. Across studies, the $t_{1/2}$ of daridorexant was between 6 h and 10 h for the 50 mg dose.

Special Populations / Intrinsic Factors

The impact of liver function on the pharmacokinetics of daridorexant following a single dose of 25 mg daridorexant was investigated in a dedicated study in subjects with normal hepatic function and mild to moderate hepatic impairment. Mild and moderate hepatic impairment resulted in a decrease of daridorexant $AUC_{0-\infty}$ and C_{max} between 25% and 50% and a delayed T_{max}. The half-life was doubled in patients with moderate hepatic impairment, which may lead to a higher extent of accumulation following multiple doses. Cu/C of daridorexant increased 1.6-fold and 2.3-fold in mild and moderate hepatic impairment, respectively, compared to healthy subjects, indicating that the unbound fraction of daridorexant was affected by increasing hepatic impairment. No patients with severe hepatic impairment were included. Based on these findings, the administration of 25 mg, half of the therapeutic dose, is recommended for patients with moderate hepatic impairment.

The impact of kidney function on the pharmacokinetics of daridorexant following a single dose of 25 mg daridorexant was investigated in a dedicated study in subjects with severe renal impairment. In view of the predominant biliary excretion of daridorexant, the reduced study design can be accepted. Whereas C_{max} remained unchanged, the AUCs were slightly increased in subjects with severe renal impairment. Overall, the exposures were comparable, although the variability was rather high. No impact on protein binding was observed. No dose adjustment is necessary for any degree of renal impairment.

Slightly higher daridorexant exposures, in particular C_{max}, were observed in Japanese subjects. These differences were primarily due to body weight.

Using data from 13 Phase 1, two Phase 2, and two Phase 3 studies (1486 patients and 412 healthy subjects), a population PK analysis was conducted to identify factors that account for variability of the daridorexant PK. The PK of daridorexant was well described by a two-compartment population PK model, with bioavailability reduced with higher doses, linear absorption, and nonlinear elimination at high concentrations associated with doses higher than 50 mg. Bioavailability, food status on absorption lag time and absorption rate constant, time of drug administration (morning, evening) on absorption rate constant, lean body weight on central volume of distribution and elimination parameter Km, fat mass on peripheral volume of distribution and inter-compartmental drug transfer (Q), age, and alkaline phosphatase (ALP) on the elimination parameter Km were identified as statistically significant covariates. Other covariates such as disease status, hepatic impairment, renal impairment, study identifier, transformed HI (healthy and mild hepatic impairment pooled), bilirubin, creatine clearance (CLCR), race and sex, were not found to be significant.

Simulations with the final model showed that higher age was associated with slightly higher C_{max} and slower elimination, higher fat mass with lower C_{max} and slower elimination, higher lean body weight with lower C_{max}, higher ALP levels with slower elimination, food status fed (following a standardised high-fat meal) with lower C_{max} and lower absorption and elimination, and morning drug administration with higher C_{max} than evening administration. The food status fasted and morning administration were shown to have the most pronounced effect. Overall, none of the investigated covariates requires dose adjustment.

Interactions

In vitro, daridorexant was shown to be a weak inhibitor of CYP1A2, CYP2A6, CYP2B6, and CYP2D6 (IC_{50} > 50 µM) and exhibited a more pronounced inhibitory effect on CYP2C8 (IC_{50} = 18 µM), CYP2C9 (IC_{50} = 19 µM), CYP2C19 (IC_{50} = 8.2 µM), and CYP3A4 (IC_{50} = 15 µM and 7.3 µM). Time-dependent inhibition in the presence of NAPDH was only observed on CYP3A4. The metabolites showed a similar inhibitory pattern; however, the effects were generally weaker. *In vitro*, daridorexant and its

metabolites activated human PXR in a concentration-dependent manner. Daridorexant induced the expression of CYP3A4, CYP2C9 and CYP2B6 but not CYP1A2 mRNA. M1 and M3 induced CYP2B6 mRNA expression, whereas none of the metabolites induced CYP1A2. Since no inductive effect has been shown on CYP3A4 *in vivo*, CYP2C was not investigated.

Daridorexant was not a substrate of P-gp, BCRP or the hepatic uptake transporters OATP1B1 and OATP1B3. Renal transporters including OAT, OCT, and MATE were not investigated, which is acceptable considering that very little parent drug is excreted in urine. *In vitro*, daridorexant inhibited BCRP (IC_{50} = 3.0 µM), MATE1 (IC_{50} = 9.7 µM), MATE2-K (IC_{50} = 8.4 µM), OATP1B1 (IC_{50} = 11 µM), OATP1B1 (IC_{50} = 16 µM) and P-gp (IC_{50} = 24/21 µM). Weak or no inhibition on OAT1/3 and OCT1/2 was observed (IC_{50} > 30 µM). The metabolites exhibited generally weaker transporter inhibition except for M1 on OATP1B1 (IC_{50} = 4.5 µM) and M1/M3 on OCT1 (IC_{50} = 0.5/8.0 µM).

The Applicant conducted the *in vitro* DDI risk assessment for the relevant enzymes and transporters at adequate concentrations of daridorexant and its metabolites. Based on these *in vitro* findings, four clinical DDI studies were conducted to investigate the impact of (1) CYP3A4 inhibition and induction on the PK of daridorexant as well as (2) daridorexant and its metabolites on CYP3A4 and BCRP substrates. Furthermore, the impact of the gastric pH-modifier famotidine on the PK of daridorexant was investigated since the solubility of daridorexant is pH-dependent (see *Biopharmaceutical Development*).

Co-administration with diltiazem, a moderate CYP3A inhibitor, caused increases of daridorexant C_{max} and $AUC_{0-\infty}$ by 40% and 140%, respectively. On the other hand, daridorexant C_{max} and $AUC_{0-\infty}$ decreased by 35% and 61%, respectively, when co-administered with efavirenz, a moderate CYP3A4 inducer. No effect of alcohol and citalopram on the PK of daridorexant was observed in two PD interaction studies (see *Pharmacodynamic Interactions*).

Co-administration with daridorexant did not have a relevant impact on the exposures of midazolam, a substrate for CYP3A4, and rosuvastatin, a substrate of BCRP. As required by current regulatory guidelines, daridorexant as perpetrator was investigated at steady state, but not with the highest therapeutic dose. Two clinical DDI studies with midazolam and rosuvastatin, respectively, co-administered with 50 mg daridorexant will be conducted (*stipulation*).

Based on these findings, only half of the dose, i.e. 25 mg, is recommended when daridorexant is co-administered with a moderate CYP3A4 inhibitor. The co-administration of a strong CYP3A4 inhibitor is contraindicated. The co-administration of a moderate or strong CYP3A4 inducer may impair the efficacy.

Ultimately, there remains the risk of clinical interaction with a P-gp or a CYP2C9 substrate. Two clinical DDI studies with a P-gp and a CYP2C9 substrate, respectively, will be conducted (*stipulation*).

Mechanism of Action and Primary Pharmacology

Daridorexant is a potent and selective orexin receptor antagonist that inhibits the actions of orexin neuropeptides at both orexin-1 and orexin-2 receptors. The orexin neuropeptides are involved in the regulation of arousal, wakefulness, and appetite.

The pharmacological effect is primarily exhibited by the parent drug. The major metabolites M1, M3, and M10 showed an 8- to 1545-fold lower inhibitory potency on both OX1 and OX2 human receptors.

The PD of daridorexant was investigated in healthy subjects. Dose-dependent effects in terms of maximal effect and the return to baseline on the CNS (reduced vigilance, attention and alertness) as well as on visuomotor coordination and postural stability (decreased saccadic peak velocity and adaptive tracking performance, as well as increased body sway) were observed starting at 25 mg. No significant impact of sex or age on the PD parameters was observed.

Secondary Pharmacology (Safety)

No prolongation of the QTc interval was observed following single therapeutic and supratherapeutic doses of 50 mg and 200 mg daridorexant in a placebo-controlled thorough QT study with moxifloxacin.

A human abuse potential (HAP) study was conducted in healthy recreational drug users. The primary endpoint, drug-liking VAS E_{max} of daridorexant, increased in a dose-dependent manner as compared

to placebo. However, 50 mg daridorexant showed significantly less drug liking compared to supratherapeutic doses of the active comparators suvorexant (150 mg) and zolpidem (30 mg). No significant differences compared to suvorexant and zolpidem were observed at daridorexant doses of 100 mg and 150 mg. A similar pattern was observed for the secondary endpoints.

Driving performance was investigated in a dedicated study in healthy middle-aged and elderly subjects including a placebo and active control. The primary endpoint was defined as the difference in standard deviation of lateral position (SDLP) between 50 mg and 100 mg daridorexant and placebo using the clinically relevant pre-specified threshold of 2.6 cm. Dose-dependent increases of the placebo-corrected LSM SDLP after single-dose administration of daridorexant were observed, with the upper bound of the 97.5% CIs of the LSM above the threshold for both doses. After multiple 50 mg and 100 mg doses, the upper bound of the 97.5% CIs of the LSM was below the threshold of 2.6 cm for both doses. In order to minimise this risk, a period of approximately 9 hours is recommended between taking daridorexant and driving or using machines.

Pharmacodynamic Interactions with other Medicinal Products or Substances

The impact of co-administration of daridorexant and ethanol on the PD was investigated in healthy subjects. Daridorexant administered together with ethanol did not have an impact on the VAS mood and calmness, nor did it further decrease smooth pursuit or the VAS alcohol intoxication compared to ethanol alone. Co-administration led to a numerically greater impairment on SPV, body sway, the VAS alertness, and adaptive tracking compared to daridorexant alone. However, there was no indication that the effects were supra-additive (synergistic).

The impact of co-administration of daridorexant and citalopram, an SSRI antidepressant, on the PD was investigated in healthy subjects. When compared to daridorexant alone, co-administration of a single dose of citalopram with daridorexant resulted in a significantly improved digit symbol substitution test (DSST) performance. No significant treatment effects were observed for all other PD parameters. When compared to daridorexant alone, a significant increase in saccadic peak velocity and DSST, as well as significant decreases in body sway and simple reaction time, were observed following the co-administration of daridorexant and citalopram at steady state, suggesting a more pronounced effect when daridorexant is administered alone. Co-administration of daridorexant and citalopram at steady state resulted in a decrease in the performance of the unstable tracking task and on the VAS alertness score, as well as a significant increase in the KSS score compared to daridorexant alone. No treatment effect was observed for the VAS mood and the VAS calmness.

6.2 Dose finding and dose recommendation

Dose finding was performed in early clinical pharmacology studies based on PK/PD and safety in healthy subjects, as well as in patients with insomnia disorder in the phase 2 studies 201 (adults) and 202 (elderly). Based on the early phase 1 investigations, doses from 5, 10, 25 and 50 mg were selected for the phase 2 dose-ranging studies, while the 75 mg and higher doses were abandoned due to increased incidences of AEs of somnolence, muscle weakness and sleep paralysis.

6.3 Efficacy

Two almost identical pivotal phase 3 studies were performed over 3 months of double-blind treatment in adult patients with insomnia disorder. For 25 and 50 mg daridorexant given once daily in the evening for 12 weeks, statistically significant differences vs. placebo were shown in the co-primary endpoints “latency to persistent sleep” (LPS) and “wake after sleep onset” (WASO) at the timepoints of 1 month and 3 months in study 301. These endpoints were objectively measured by polysomnography (PSG). A dose effect with higher effects for the 50 mg dose was observed for WASO and was less pronounced for the LPS endpoint.

In study 302, the effects of the 25 mg dose on the co-primary endpoints LPS and WASO were comparable to the effects of the same dose in 301, while only small numerical differences vs. placebo for LPS and WASO were noted for the 10 mg dose. The treatment differences vs. placebo in the

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

reduction of LPS ranged from 7 to 12 minutes for the 25 and the 50 mg doses, while the differences vs. placebo in reduction of WASO were between 12 and 23 minutes for the 25 and the 50 mg doses (similar results for the two timepoints at 1 and 3 months). Effects on the self-assessed secondary endpoint of subjective total sleep time (sTST) were also statistically significant for the 25 and 50 mg doses, with increases in sTST between 13 and 22 minutes vs. placebo. No relevant differences in efficacy were seen in subgroups for age (elderly with similar effect), sex, race or region.

With the responses to the List of Questions, responder analyses were submitted to support the clinical relevance of the observed effects on the main sleep parameters LPS, WASO and TST at 1 and 3 months. For the 50 mg dose, responder differences versus placebo ranged from 10% to 20%, while lower differences in responder rates of around 5-10% versus placebo were observed for the 25 mg dose. Overall, the 25 mg dose should be considered as an optional dose, e.g. if the standard dose is not tolerated.

The results of the double-blind and controlled extension study 303 were used to support a treatment duration of up to 12 months by the applicant.

6.4 Safety

The most common treatment emergent adverse events (TEAEs) in the pivotal studies 301 and 302 were nasopharyngitis, headache, accidental overdose, fatigue, dizziness, nausea, and somnolence. Most TEAEs were of mild to moderate intensity. Events that were infrequent but regarded as related to the study drug were sleep paralysis and sleep-related hallucinations.

Serious adverse events (SAEs) occurred with low frequency in the pivotal studies and were single events without a clear pattern, and the overall highest frequency of SAEs was in the placebo group. However, some of the SAEs reported in study 303, like confusional state, lethargy and nausea, could be judged as possibly related to daridorexant treatment.

Adverse events related to excessive daytime sleepiness, complex sleep behaviour, including sleep paralysis and hallucinations, and cataplexy were rare in the pivotal studies. They were reviewed by an independent safety board, and none of them was judged as “true narcolepsy phenotype”.

In the whole daridorexant development program, four deaths were reported, all in the active daridorexant groups, three of which were treatment-emergent, and one of which occurred several weeks after the end of study due to lung cancer. None of the four events was judged as treatment-related, which appears comprehensible based on the reported confounding risk factors. No relevant effects on vital signs (heart rate, systolic and diastolic blood pressure) have been observed, and no increased risk for cardiovascular TEAEs has been documented in the clinical studies.

Uncertainties about unfavourable effects include the potential for withdrawal symptoms and also a possible rebound of insomnia, since the withdrawal symptoms were assessed during the 7-day placebo run-out phase, which is considered quite short to detect possible delayed withdrawal effects. With regard to a driving impairment, a 9h interval between intake of daridorexant and driving is now recommended in the information for healthcare professionals.

6.5 Final clinical and clinical pharmacology benefit risk assessment

Daridorexant is a dual orexin-receptor-antagonist administered in tablet form for the treatment of insomnia. It binds to orexin receptors 1 and 2 and acts as a competitive antagonist.

The clinical pharmacology package for daridorexant was extensive and covered all the relevant aspects. Four clinical interaction studies will be conducted to exclude potential interactions (*stipulation*). The administration of 25 mg, half of the therapeutic dose, is recommended for patients with moderate hepatic impairment. The impact of severe hepatic impairment on the PK of daridorexant was not investigated. Based on clinical DDI studies, a dose reduction by half is recommended when daridorexant is co-administered with a moderate CYP3A4 inhibitor. The co-administration of a strong CYP3A4 inhibitor is contraindicated. Co-administration of a moderate or strong CYP3A4 inducer may impair the efficacy.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

The applicant studied efficacy and safety of 10, 25 and 50 mg daridorexant in two randomised, double-blind, placebo-controlled clinical phase 3 trials in patients with at least moderate insomnia disorder according to DSM-5. Statistically significant and clinically relevant effects on the latency to sleep onset (LPS) and sleep maintenance (wake after sleep onset, WASO, and total sleep time, TST) were shown for 50 mg and mostly for 25 mg.

Most TEAEs were of mild or moderate intensity. Events that were infrequent but regarded as related to the study drug were sleep paralysis and sleep-related hallucinations. Adverse events related to excessive daytime sleepiness, complex sleep behaviour including sleep paralysis and hallucinations, and cataplexy were rare in the pivotal studies.

Based on the currently available data, the benefit-risk ratio for daridorexant in the treatment of insomnia disorder in adult patients is regarded as favourable.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

7 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

8 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for QUVIVIQ was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the information for healthcare professionals approved in one of the official Swiss languages.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

▼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. QUVIVIQ can be administered with CYP3A4 substrates (e.g., simvastatin, ticagrelor) without dose adjustment.
In the absence of clinical data with 50 mg, caution should be used in case of concomitant administration with CYP3A4 substrates, including oral contraceptives, with close safety and efficacy monitoring in case of medicinal products with a narrow therapeutic index that cannot be avoided.
In the absence of clinical data, caution should be used in case of concomitant administration with CYP2C9 substrates with close efficacy monitoring in case of medicinal products with a narrow therapeutic index.

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 a clinical study conducted in healthy subjects receiving daridorexant and rosuvastatin, a BCRP substrate, daridorexant at a dose of 25 mg (steady state) did not affect the PK of rosuvastatin (decrease of both C_{max} and $AUC_{0-\infty}$ by 7%), indicating an absence of inhibition of BCRP at this dose. In the absence of clinical data at 50 mg, simultaneous administration of QUVIVIQ with BCRP substrates (e.g., rosuvastatin, imatinib) should be handled with caution.
In the absence of clinical data, simultaneous administration of QUVIVIQ with P-gp substrates (e.g., digoxin, dabigatran) should be handled with caution, with close monitoring in case of medicinal products with a narrow therapeutic index (e.g., digoxin).

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 490 subjects were treated with daridorexant for at least 6 months and 314 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).
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.

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: other hypnotics and sedatives, ATC code: not yet assigned.

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

Date of revision of the text

May 2022