# SUMMARY OF THE RISK MANAGEMENT PLAN (RMP) FOR QUVIVIQ® (DARIDOREXANT)

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Disclaimer:

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of QUVIVIQ is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g., by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of QUVIVIQ in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Idorsia Pharmaceuticals Ltd. is fully responsible for the accuracy and correctness of the content of the published summary RMP of QUVIVIQ.

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## Summary of the risk management plan

This is a summary of the risk management plan (RMP) for QUVIVIQ. The RMP details important risks of QUVIVIQ, how these risks can be minimised, and how more information will be obtained about QUVIVIQ's risks and uncertainties (missing information).

QUVIVIQ's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how QUVIVIQ should be used.

This summary of the RMP for QUVIVIQ should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of QUVIVIQ's RMP.

## I. The medicine and what it is used for

QUVIVIQ is authorised for the treatment of adult patients with insomnia characterised by symptoms present for at least 3 months and considerable impact on daytime functioning. It contains daridorexant as the active substance and it is given as film-coated tablets for oral use.

## II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of QUVIVIQ, together with measures to minimise such risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals.
- Important advice on the medicine's packaging.
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly.
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute ***routine risk minimisation*** measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action

can be taken as necessary. These measures constitute ***routine pharmacovigilance activities***.

If important information that may affect the safe use of QUVIVIQ is not yet available, it is listed under 'missing information' below.

### *II.A List of important risks and missing information*

Important risks of QUVIVIQ are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken.

Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of QUVIVIQ. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected.

| **List of important risks and missing information** | |
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| Important identified risks | None |
| Important potential risks | Potential for drug abuse.<br>Suicidal behaviour in high-risk patients (with a medical history of depression or other psychiatric disorders). |
| Missing information | Use in pregnant women.<br>Use in breast-feeding women.<br>Use in patients > 75 years |

### *II.B Summary of important risks*

| **Important potential risk: potential for drug abuse** | |
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| Evidence for linking the risk to the medicine | The risk of hypnotic drug abuse in primary insomniacs has been shown not to be significant [Mendelson 2004[1]].<br>Abuse potential properties were reported for the two dual orexin receptor antagonists (DORAs) marketed in other regions, in dedicated human abuse potential (HAP) studies.<br>The abuse potential of daridorexant was evaluated in preclinical models, recreational sedative drug users and insomnia subjects. |

[1] Mendelson WB, Roth T, Cassella J, Roehrs T, Walsh JK, Woods JH, et al. The treatment of chronic insomnia: drug indications, chronic use and abuse liability. Summary of a 2001 New Clinical Drug Evaluation Unit meeting symposium. Sleep Med Rev. 2004;8(1):7−17.

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| | Daridorexant showed no signs indicative of abuse potential or physical dependence in rats.<br><br>In a clinical pharmacology study to evaluate drug-liking properties of daridorexant, the abuse potential of single doses of daridorexant (recommended therapeutic dose of 50 mg, supratherapeutic doses of 100 and 150 mg) was investigated in 72 healthy recreational drug users, in comparison to supratherapeutic doses of suvorexant (150 mg) and zolpidem (30 mg). The primary endpoint was the maximum possible effect ($E_{max}$) on the bipolar Drug Liking visual analogue scale (VAS; 0-100).<br><br>Daridorexant exhibited a dose-dependent maximal effect in the drug-liking VAS score that was higher than that of placebo. At the therapeutic dose of 50 mg, the effect of daridorexant was lower than those of both control drugs used at the supratherapeutic doses of 150 mg for suvorexant and 30 mg for zolpidem. At the supratherapeutic doses of 100 and 150 mg, the effect of daridorexant was similar to those of the control drugs. Such dose-related patterns were also observed for most secondary pharmacodynamic (PD) endpoints, indicating a lower abuse potential of daridorexant at the dose of 50 mg compared to supratherapeutic doses of zolpidem and suvorexant.<br><br>The treatment-emergent adverse events (TEAEs) suggestive of euphoria, such as euphoric mood and feeling abnormal, were less frequent at therapeutic and supratherapeutic doses of daridorexant as compared to suvorexant and zolpidem. In addition, daridorexant showed fewer perceptual alterations and less impairment of cognitive function compared to zolpidem (at all doses of daridorexant) and suvorexant (at 50 mg of daridorexant only).<br><br>The translatability and relevance of these data from recreational sedative drug users to the general population as well as for patients with insomnia will need to be further explored based on post-marketing data.<br><br>In studies 301, 302, and 303, no events denoting abuse potential, including adverse events (AEs) of euphoria, were retrieved via a broad MedDRA search. The nature of other reported AEs during the Phase 3 studies did not show any evidence or pattern suggestive of abuse potential, and there was no evidence of withdrawal symptoms. |
| Risk factors and risk groups | Subjects with a history of drug abuse (particularly sedatives) and those who may use daridorexant in combination with alcohol or other abused drugs. |
| Risk minimisation measures | Routine risk minimisation measures:<br>– SmPC section 4.4<br>– SmPC section 4.2<br>– Product Information Leaflet (PIL) section 2<br>– Limited pack sizes<br>– Medicinal product subject to medical prescription<br><br>Additional risk minimisation measures:<br><br>None. |

| **Important potential risk: suicidal behaviour in high-risk patients (with a medical history of depression or other psychiatric disorders)** | |
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| Evidence for linking the risk to the medicine | In clinical trials of daridorexant in patients with insomnia, depression and suicidal ideation/ behaviour risks were assessed both through reports of any AEs pertaining to depression and suicide/self-injury, and any changes in Columbia-Suicide Severity Rating Scale® (C-SSRS®) scores. Reported events pertaining to suicide/self-injury were also adjudicated by an Independent Safety Board (ISB).<br><br>Based on C-SSRS® scores, there were no subjects with suicidal ideation, suicidal behaviour, and/or self-injurious behaviour without suicidal intent during the double-blind treatment period of daridorexant studies.<br><br>Isolated cases of suicidal ideation were reported, equally distributed across treatment groups including placebo, for subjects with a psychiatric medical history (depression, paranoid schizophrenia) and/or acute extenuating circumstances (family/financial stress, illicit drug use). A causal relationship to the study drug could not be ascertained due to significant confounding factors in all cases.<br><br>Furthermore, there was no evidence of any worsening of depression in subjects with medical history or stable concomitant depression at baseline.<br><br>Worsening of depression and suicidal ideation were observed in clinical studies for the two marketed DORAs (suvorexant and lemborexant).<br><br>Suicidal behaviour in high-risk patients (with medical history of depression or other psychiatric disorders) is conservatively considered an important potential risk for daridorexant, based on the evidence that insomnia itself, as well as the use of other hypnotic medications, represent an increased risk for suicidal behaviour. |
| Risk factors and risk groups | Subjects with a history of depression or other psychological disorders associated with risk of suicidal ideation/behaviour. |
| Risk minimisation measures | Routine risk minimisation measures:<br>– SmPC section 4.4<br>– SmPC section 4.2<br>– PIL section 2<br>– Medicinal product subject to medical prescription<br><br>Additional risk minimisation measures:<br><br>None. |

| **Missing information: use in pregnant women** | |
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| Risk minimisation measures | Routine risk minimisation measures:<br>– SmPC sections 4.6 and 5.3<br>– PIL section 2<br>– Medicinal product subject to medical prescription<br>Additional risk minimisation measures:<br>None. |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities:<br>QUVIVIQ pregnancy registry<br>See section II.C of this summary for an overview of the post-authorisation development plan. |

| **Missing information: use in breast-feeding women** | |
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| Risk minimisation measures | Routine risk minimisation measures:<br>– SmPC section 4.6<br>– PIL section 2<br>– Medicinal product subject to medical prescription<br>Additional risk minimisation measures:<br>None |

| **Missing information: use in patients > 75 years** | |
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| Risk minimisation measures | Routine risk minimisation measures:<br>– SmPC section 4.4<br>– SmPC section 4.2<br>– PIL section 2<br>– Medicinal product subject to medical prescription<br>Additional risk minimisation measures:<br>None |

***II.C Post-authorisation development plan***

**II.C.1 Studies which are conditions of the marketing authorisation**

There are no studies which are conditions of the marketing authorisation or specific obligations of QUVIVIQ.

**II.C.2 Other studies in post-authorisation development plan**

QUVIVIQ Pregnancy Registry

Purpose of the study: Animal studies did not indicate harmful effects with respect to reproductive toxicity. However, there are currently no data on the use of daridorexant in pregnant women. The objectives of the pregnancy registry are to investigate pregnancy, neonatal, and infant outcomes of women exposed to QUVIVIQ during their pregnancy, compared to an unexposed control group.