

Evidence Dossier to Support Formulary Application:

QUVIVIQ™ ▼ (daridorexant) 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.¹

The purpose of this document is to provide a repository of data to prepare clinicians, pharmacists and budget holders for the availability of daridorexant in the UK.

Daridorexant has been reviewed and recommended as a treatment option by NICE in their single technology appraisal '*Daridorexant for treating insomnia disorder [ID3774]*'.² Data provided in this document mirrors that submitted to NICE, and is hoped to allow early preparation of local formulary applications, and minimise delays in patient access following NICE's decision.

This document is structured such that key information for formulary application is given in bullets at the start of each chapter, with additional detailed commentary provided thereafter.

For further information please contact: peter.graham@idorsia.com

Prescribing Information and Adverse Event reporting can be found on the final page of this document

Table of Contents

Executive Summary.....	3
Daridorexant Medicine Details	4
Disease Characteristics.....	7
Burden of Disease	11
Clinical Pathway.....	13
Limitations of current care	17
Clinical Evidence	20
Economic Impact	30
References.....	33

Executive Summary

Insomnia is associated with a number of symptoms which can drastically affect the patient's sense of wellbeing, perceptions of their own health, and occupational and social functioning.⁸ Patients with insomnia suffer from both night-time symptoms and daytime functioning impairment, affecting both subjective and objective dimensions of health.^{8,9} Impaired daytime functioning due to insomnia increases the risk of errors or accidents, impacts task performance and negatively impacts social life, relationships, and family life.¹⁰ If left untreated, insomnia can increase the risk of depression and anxiety, and in the long term, diabetes and cardiovascular disease (CVD).⁹ Insomnia has been shown to have a significant impact on both the NHS and the broader economy, with studies estimating that the reduction in our population's total QALY count due to insomnia, may be greater than that associated with hypertension or arthritis.³

Insomnia disorder, also known as chronic insomnia, or long-term insomnia in the case of NICE, is characterised by type, frequency and duration of symptoms, and is commonly categorised using diagnostic classification systems from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5; 2013),¹¹ and the International Classification of Sleep Disorders, Third Edition (ICSD-3; 2014).¹² Insomnia may be further categorised into acute or chronic illness.¹⁰ The UK prevalence of chronic insomnia, in which patients experience symptoms at least three times per week and for at least 6 months in the past year (i.e. the DSM-5 criteria), is estimated at 7.3%.^{14,15,16}

The negative impact of chronic insomnia on HRQoL was quantified using the UK subset of the 2020 National Health and Wellness Survey (NHWS), in which the mean EQ-5D utility score of respondents with insomnia symptoms was significantly lower than that of the general cohort (n=8,280) (0.68 [0.25] vs 0.82 [0.21], p<0.001).¹⁶

The economic burden of insomnia is substantial. Patients with increasing insomnia severity, described by their Insomnia Severity Index (ISI®) score, have been shown to demand more NHS care (via GP, hospital, or A+E visits), than those without symptoms,¹⁶ while off-label use of existing pharmacotherapy for durations longer than recommended,²⁴ is also likely to add to the financial burden on the NHS. Substantial indirect costs associated with insomnia-related absenteeism, presenteeism, and work-productivity have also been reported.^{29,30}

Many patients initially self-treat using a range of strategies including improved sleep-hygiene, diet, exercise, or over-the-counter medication – however the benefits of these approaches are often transient. Despite this, many GPs use a similar strategy upon initial diagnosis.²⁴

The non-pharmacological approach of cognitive behavioural therapy for insomnia (CBTi) is the recommended first-line treatment for chronic insomnia in the UK, however many people are unable to access or complete CBTi courses due to limitations in access,³⁵ course duration,³⁶ adherence,³⁷ consistency of delivery and results,³⁷ and the impact of the required sleep restriction.³⁹

Pharmacotherapies (including Z-drugs, benzodiazepines, and melatonin) are only recommended for a short duration, and in treatment naïve patients when CBTi is unavailable, unsuitable or ineffective. Notably, benzodiazepines and Z-drugs should be restricted to the shortest possible duration (<4 weeks) due to safety risks, particularly dependence, associated with prolonged use.^{10,23,27} Prolonged release

melatonin is only indicated for the short-term treatment of primary insomnia characterised by poor quality of sleep, in patients who are aged 55 or over.

Daridorexant is the first dual orexin receptor antagonist (DORA) to be approved in the UK and Europe for the treatment of chronic insomnia. It is an evidence-based treatment with established efficacy and safety for up to one year.^{43,44} The clinical trials of daridorexant demonstrated improved night- and day-time symptom control of insomnia in adult and elderly patients with a favourable safety profile.

Results from the phase III confirmatory study (301) and extension study (303) demonstrated that treatment with daridorexant 50 mg once daily in patients with chronic insomnia was superior to placebo for the primary endpoints of objective sleep induction (*latency to persistent sleep - LPS*) and maintenance (*wakefulness after sleep onset - WASO*).^{43,44} Superiority over placebo was also demonstrated for key secondary endpoints of patient reported sleep quantity (*subjective total sleep time - sTST*) and daytime functioning scores (*insomnia daytime symptoms and impacts questionnaire - IDSIQ*).^{43,44} The benefits of daridorexant on patient-reported sleep quantity and daytime functioning were sustained for up to a year, as shown by the improved sTST and IDSIQ sleepiness domain score after 6, 9 and 12 months of treatment.^{43,44} Results are notable for two reasons; firstly, symptom improvement was achieved despite placebo treatment being well documented as a driver of improvement in insomnia trials,⁴ and secondly the NICE Committee noted that daridorexant has no approved active comparator licensed and reimbursed in the UK.²

A major challenge in patients with chronic insomnia is to reverse impaired daytime functioning – a limitation of most existing pharmacotherapies.⁵ Subjects in the daridorexant 50 mg group reported improvements in all aspects of daytime functioning compared to placebo in both the 301 and 303 studies, as assessed by IDSIQ total score, mood domain score, alert/cognition domain score, and sleepiness domain score.^{43,44} The ability to reverse impaired daytime functioning demonstrated by daridorexant addresses an important gap in the current insomnia disorder treatment landscape.

In terms of safety, daridorexant was well tolerated in both adult and elderly patients.^{43,44}

Daridorexant is an affordable addition to local treatment pathways. In an example ICS population of 100,000 residents, treatment of 47 eligible patients is expected to cost £12,765 in year one, rising to £71,702 in year five, when 264 eligible patients are expected to receive treatment.

To present a conservative budget impact scenario, additional savings arising from the introduction of daridorexant are not quantified in this document. However the above costs are likely to be an over-estimate based on the cost of displaced medicines (including Z-drugs, benzodiazepines, or melatonin) currently used off-label to manage longer term insomnia symptoms, and a reduction in the costs of dependency/addiction which is a major issue with chronic off-label use of BZDs and Z-drugs, as well as both direct (*GP, hospitalisation, A+E*) and indirect (*absenteeism, presenteeism, and work productivity*) costs, expected as patients move to lower categories of insomnia severity.

NICE recommends that daridorexant can be used in primary care for treating insomnia in adults with symptoms lasting for 3 nights or more per week for at least 3 months, and whose daytime functioning is considerably affected, only if CBTi has been tried but not worked, or CBTi is not available or is unsuitable.²

Daridorexant Medicine Details

Indication ¹	QUVIVIQ® (daridorexant) 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.
Mode of action ¹	Daridorexant is a dual orexin receptor antagonist, acting on both orexin 1 and orexin 2 receptors and equipotent on both. The orexin neuropeptides (orexin A and orexin B) act on orexin receptors to promote wakefulness. Daridorexant antagonises the activation of orexin receptors by the orexin neuropeptides and consequently decreases the wake drive, allowing sleep to occur, without altering the proportion of sleep stages (as assessed by electroencephalographic recording in rodents or polysomnography in patients with insomnia).
Therapeutic class	Sleep Initiation and Maintenance Disorders
ATC code	N05CJ03 – recently created to describe orexin receptor agonists
Regulatory Status	Quviviq 25mg and 50mg have been authorised by the MHRA for use in Great Britain, based on the EC Decision Reliance Procedure following the EC decision on 29 April 2022 (EMA/H/C/0534/0000). ⁶
Dosing ¹	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. While this is not the recommended treatment dose, it may be appropriate for treating patients with moderate hepatic dysfunction or when taking moderate CYP3A4 inhibitors. Please see SMPC sections 4.4 and 4.5.¹ The maximum daily dose is 50 mg, and daridorexant 25mg should not be considered a titration dose, rather an option for patients with moderate hepatic dysfunction or when taking moderate CYP3A4 inhibitors. The treatment duration should be as short as possible. The appropriateness of continued treatment should be assessed within 3 months and periodically thereafter. Clinical data are available for up to 12 months of continuous treatment. Treatment can be stopped without down-titration. As there is no risk of withdrawal or rebound effect, treatment can be stopped without specific stopping rules. Prescribers can be confident of stopping daridorexant to assess whether there is still a need to continue, and if insomnia returns that the beneficial effects of daridorexant will resume upon treatment re-initiation.⁷
Presentation ¹	Daridorexant is available as 25 mg and 50 mg film-coated tablets.
Contraindications ¹	• Hypersensitivity to the active substance or to any of the excipients. • Narcolepsy • Concomitant use with strong CYP3A4 inhibitors
Special warnings and precautions for use ¹	Please refer to the SMPC for details of special warnings and precautions for use regarding: • Elderly • CNS-depressant effects • Sleep paralysis, hallucinations and cataplexy-like symptoms • Worsening of depression and suicidal ideation

	• Patients with psychiatric co-morbidities • Patients with compromised respiratory function • Potential for abuse and dependence • Hepatic impairment
Concomitant use with other medicinal products ¹	• <u>CYP3A4 inhibitors</u>: In patients taking moderate CYP3A4 inhibitors (e.g., erythromycin, ciprofloxacin, cyclosporine), the recommended dose of QUVIVIQ is 25 mg. • <u>CYP3A4 inducers</u>: concomitant use with a moderate or strong CYP3A4 inducer substantially decreases exposure to daridorexant, which may reduce efficacy • <u>Gastric pH-modifiers</u>: The solubility of daridorexant is pH-dependent. In healthy subjects, co-administration with famotidine (40 mg), an inhibitor of gastric acid secretion, decreased daridorexant C_{max} by 39% while AUC remained unchanged. No dose adjustment is required when QUVIVIQ is used concomitantly with treatments that reduce gastric acidity. The consumption of grapefruit or grapefruit juice in the evening should be avoided. • <u>Citalopram</u>: 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. • The effect of daridorexant on the pharmacokinetics of other medicinal products is described in the SMPC (section 4.5)
Cost	£1.40 per day
Service Implications	No additional tests or investigations are required for identification of the population for daridorexant administration.
Areas of use (supported by NICE) ²	• As a second-line treatment option when digital or face-to-face CBTi has been tried but not worked, or as maintenance treatment for managing longer-term symptoms. • As a first-line treatment option when CBTi is not available or unsuitable.
NICE endorsement	Daridorexant is recommended for treating insomnia in adults with symptoms lasting for 3 nights or more per week for at least 3 months, and whose daytime functioning is considerably affected, only if: • cognitive behavioural therapy for insomnia (CBTi) has been tried but not worked, or • CBTi is not available or is unsuitable. The length of treatment should be as short as possible. Treatment with daridorexant should be assessed within 3 months of starting and should be stopped in people whose long-term insomnia has not responded adequately. If treatment is continued, assess whether it is still working at regular intervals. The most likely cost-effectiveness estimate is within what NICE considers an acceptable use of NHS resources. So, daridorexant is recommended for routine use in the NHS.²

Disease Characteristics

Key Facts:

- Insomnia is associated with a number of symptoms which can drastically affect the patient's sense of wellbeing, perceptions of their own health, occupational, and social functioning.⁸
- Patients with insomnia suffer from both night-time symptoms and daytime functioning impairment, affecting subjective and objective dimensions of health.^{8,9}
- While identifying and treating potential underlying conditions is important, the key priority should be to manage insomnia regardless of the underlying cause
- Impaired daytime functioning due to insomnia increases the risk of errors or accidents, impacts task performance and negatively impacts social life, relationships, and family life.¹⁰ If left untreated, insomnia can increase the risk of depression and anxiety, and in the long term, diabetes and cardiovascular disease (CVD).¹⁰
- Insomnia has been shown to have a significant impact on both NHS and the broader economy, and estimated to reduce our population's QALY count by more than hypertension or arthritis.³
- Insomnia disorder is characterised by type, frequency and duration of symptoms using the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5; 2013),¹¹ and the International Classification of Sleep Disorders, Third Edition (ICSD-3; 2014)¹² diagnostic classification systems, and may be further categorised into acute and chronic illness.¹¹
- The DSM-5 and the ICSD-3 recommends that insomnia should be considered as an independent disorder, regardless of the presence of comorbidities or any ongoing physical or mental disorder, including any concurrent sleep disorder.¹²
- The Cerner Enviza National Health and Well-being Survey (NHWS) is a large, nationally representative, self-administered, internet-based questionnaire involving adults (aged 18 years or older) which included 10,408 respondents in the UK.^{14,15} The prevalence of insomnia disorder (aligned to the DSM-5 criteria), was estimated based on the number of respondents who experienced insomnia symptoms at least four times per week and for at least 6 months in the past year, suggesting a prevalence rate of 7.3%.¹⁶

Disease overview

In general practice, clinicians frequently encounter patients with sleep disorders related to sleep initiation or maintenance, often referred to as insomnia.¹⁷ Insomnia may be a primary disorder (a syndrome) or secondary to a variety of physical or psychiatric illnesses (e.g., sleep apnoea, depression, anxiety), environmental factors (e.g., noise levels, temperature, seasonal changes) and/or psychosocial issues (e.g., current or upcoming stressors).⁸ While identifying and treating potential underlying conditions is important, the key priority should be to manage insomnia regardless of the underlying cause. Insomnia is associated with a number of symptoms which can drastically affect the patient's sense of wellbeing, perceptions of their own health, occupational, and social functioning.⁸ Patients with insomnia suffer from both night-time symptoms and daytime functioning impairment, affecting subjective and objective dimensions of health.^{8,9} Insomnia impairs

an individual's overall quality of life (QoL) by affecting physical and mental health, cognitive ability, mood, and behaviour. Moreover, impaired daytime functioning due to insomnia increases the risk of errors or accidents, impacts task performance and negatively impacts social life, relationships, and family life.¹⁰ If left untreated, insomnia can increase the risk of depression, anxiety, and in the long term, diabetes and cardiovascular disease (CVD).¹⁰

Definition of insomnia disorder

Insomnia disorder (also known as chronic insomnia or long-term insomnia) is characterised by type, frequency and duration of symptoms, typically characterised using the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5; 2013)¹¹, or the International Classification of Sleep Disorders, Third Edition (ICSD-3; 2014),¹² diagnostic classification systems:

- Insomnia is defined by the DSM-5 as dissatisfaction with sleep quantity or quality that is accompanied by one (or more) of the following symptoms: difficulty initiating and maintaining sleep, characterised by frequent awakenings or problems returning to sleep, and early morning awakenings with inability to return to sleep.¹¹ The sleep disturbance causes clinically significant distress or impairment, with detrimental effects on daytime functioning, including social, occupational, educational, academic, behavioural, or other important areas of functioning.¹³
- The ICSD-3 defines insomnia as persistent difficulty with sleep initiation, duration, consolidation or quality that occurs despite the opportunity and circumstances for sleep, resulting in some daytime functional impairment.¹² This definition of insomnia disorder is consistent with that of the International Classification of Diseases, 11th Revision.¹⁸

Based on the duration and frequency of sleep disturbance, DSM-5 and ICSD-3 further classify insomnia as acute and chronic insomnia:^{11,13}

- Acute or short-term insomnia refers to transient episodes of insomnia, with symptoms lasting <3 months, that usually occur after an emotional or psychological stress and resolve quickly once the underlying causes are addressed.
- Chronic insomnia (also referred to as insomnia disorder in this document) is defined as insomnia symptoms occurring for ≥ 3 nights per week for ≥ 3 months.

Pathogenesis

The sleep-wake cycle is regulated by homeostatic and circadian processes.¹⁹ Together with a complex interplay of neurologic, neuroanatomical, and chemical pathways, these processes achieve balance between sleep and wake.¹⁹ Therefore, any impact on these factors is anticipated to influence the sleep-wake cycle, resulting in some cases, in insomnia.¹⁹

Diagnosis

The DSM-5 and the ICSD-3 recommends that insomnia should be considered as an independent disorder, regardless of the presence of comorbidities or any ongoing physical or mental disorder,

including any concurrent sleep disorder.¹² An independent diagnosis of chronic insomnia should be made, taking into consideration the type, duration and frequency of symptoms. It is also recommended to consider the temporal relationship between the development of insomnia symptoms and those of other medical conditions, since insomnia disorder can precipitate or worsen existing comorbidities.¹²

Assessment of chronic insomnia

As per the DSM-5 definition, chronic insomnia is a subjective patient experience wherein instruments to collect patient reported outcomes (PROs) may play an important role in diagnosis and management.

Numerous PRO instruments are available to assess patients' perception of sleep problems and the associated impact on daytime functioning. Among them, the PROs described below were part of daridorexant clinical development program.

- 1) The Sleep Diary Questionnaire (SDQ)
- 2) The Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ)
- 3) Insomnia Severity Index[®] (ISI[®]).
- 4) Sheehan Disability scale[®] (SDS[®]).

Clinical guidelines do not recommend the use of any specific PRO instrument to assess insomnia symptoms in clinical practice, although some instruments are validated for use in primary care.²⁰

Epidemiology

Insomnia is more common in women than in men, and its prevalence increases with age in both sexes.⁸

Few studies have estimated the prevalence of insomnia disorder using the current DSM-5 criteria, with none found focussing on the UK population. Therefore, data from the 2020 National Health and Wellness Survey (NHWS) were utilised to estimate the prevalence of insomnia disorder in the UK.^{14,15}

The Cerner Enviza NHWS is a large, nationally representative, self-administered, internet-based questionnaire involving adults (aged 18 years or older) in the US, UK, France, Germany, Italy, Spain and Japan.^{14,15}

The 2020 NHWS data included 10,408 respondents in the UK with a mean age of 47.3 years and 53.3% were females (n=5,544). Approximately 1 in 5 respondents (21%) reported experiencing symptoms of insomnia.¹⁵ The prevalence of chronic insomnia (aligned to the DSM-5 criteria), was estimated based on the number of respondents who experienced insomnia symptoms at least four times per week and for at least 6 months in the past year, suggesting a prevalence rate of 7.3%.¹⁶

Similarly, the 2023 RAND study "The Social and economic burden of insomnia", estimates that in the UK, prevalence of insomnia symptoms is 35 – 38.6%, prevalence of clinical insomnia is 12.6 – 13.9% and prevalence of chronic insomnia is 6.8 – 14.8%, driving a significant toll on individuals' mental and physical health, quality of life and productivity.³

Risk factors

The multifactorial aetiology of insomnia involves a range of risk and lifestyle factors, including demographics, clinical, and genetic factors, with multiple psychiatric and medical conditions frequently associated with, or having reciprocal relationships with, insomnia disorder.²¹ Approximately 50% of patients with insomnia also have mood (e.g., major depressive disorder) or anxiety disorders (e.g., PTSD).^{22,23} In UK primary care, 71% of insomnia patients experience depression, while 77% experience anxiety.²⁴

Chronic insomnia is a common comorbid condition and a risk factor for chronic diseases and mortality. A meta-analysis of 14 prospective cohort studies demonstrated an increased risk of hypertension in insomnia patients compared to those without insomnia (RR=1.21, [95% CI 1.10, 1.33]).²⁵ A cross-sectional study involving 1,311 insomnia sufferers in Belgium reported that those with <6.5 hours of sleep had higher odds of having type 2 diabetes compared to those with ≥8 hours of sleep (OR=1.81, [95% CI 1.15, 2.84]).²⁶

A systematic review and meta-analysis of prospective cohort studies assessed the relationship between sleep duration, all-cause mortality and cardiovascular events.⁹ A pooled analysis of 57 studies showed that when sleep duration was <7 hours a day, all-cause mortality increases by 6% (95% CI [4 to 7%]) per 1-hour reduction in sleep duration.⁹ Similarly, an analysis of 37 studies reported a 6% (95% CI [3 to 8%]) increase in risk of cardiovascular events per 1-hour reduction in sleep duration.⁹ The findings from these studies demonstrate the increased risk of chronic diseases and mortality associated with insomnia disorder.

Despite the associated comorbidities, BAP and NICE guidelines advocate for independent diagnosis and treatment of chronic insomnia in primary care.^{10,27} Referral to a specialist should only be considered if other sleep disorders are suspected or if treatment in primary care has failed.

Burden of Disease

Key Facts:

- Insomnia is commonly linked to a diminished QOL status for both primary (syndromic) and secondary (symptomatic) insomnia, with associations to a number of adverse medical, social, and psychological detriments to quality of life (QOL).⁸ Insomnia has a large impact on an individual's ability to maintain work, physical, and social performance as well as overall quality of life.⁸
- The negative impact of insomnia disorder on HRQoL was quantified using the UK subset of the 2020 NHWS data, where mean EQ-5D utility of 2,128 respondents who reported insomnia symptoms was significantly lower than that of the general cohort (n=8,280) (0.68 [0.25] vs 0.82 [0.21], p<0.001).¹⁶
- The direct economic burden to the NHS is hard to quantify, with many costs categorised as indirect – affecting the patients ability to work and function productively.
- Patients with increasing ISI[®] score (showing their insomnia severity), have been shown to demand more NHS care (via GP, hospital or A+E visits), than those without symptoms.¹⁶
- Off-label use of existing pharmacotherapy for durations longer than recommended, is also likely to present a financial burden on the NHS.²⁴

Disease progression and mortality risk

Humanistic burden

Insomnia is commonly linked to a diminished QOL status for both primary (syndromic) and secondary (symptomatic) insomnia, with associations to a number of adverse medical, social, and psychological detriments to quality of life (QOL).⁸ Insomnia has a large impact on an individual's ability to maintain work, physical, and social performance as well as overall quality of life.⁸ Chronic insomnia is associated with considerable daytime impairment, often leading to daytime sleepiness, fatigue, and irritability which contributes to depression and anxiety.⁸ It can impact patients' ability to complete tasks and participate in activities of daily living, including an increased risk of workplace accidents.⁸ Chronic insomnia is also associated with a higher risk of falls and injuries among the elderly.²⁸ In the UK, 52% of patients reported severe impact on personal and professional life due to insomnia.²⁴

The negative impact of chronic insomnia on HRQoL was quantified using the UK subset of the 2020 NHWS data (N=10,408).¹⁶ Mean [SD] EQ-5D utility of 2,128 respondents who reported insomnia symptoms was significantly lower than that of the general cohort (n=8,280) (0.68 [0.25] vs 0.82 [0.21], p<0.001).¹⁶ Subgroup analysis showed that the impaired HRQoL was apparent regardless of insomnia disorder diagnosis or treatment status.¹⁶

Economic burden

The economic burden of chronic insomnia is challenging to quantify due to the subjective nature of the condition and its frequent occurrence together with other conditions that confer a much higher burden. The RAND 2023 economic predictions estimated the economic loss of insufficient sleep at 1.31% of GDP, or £34bn.³

The economic burden of chronic insomnia has been quantified using data from the NHWS. Analysis of the UK subset of NHWS data showed that healthcare resource utilisation (HCRU) increased with increasing ISI[®] score, indicating that economic burden increases with worsening insomnia disorder.¹⁶

Productivity loss is the main driver of the economic burden of insomnia disorder.^{29,30} Data from the Work Productivity and Activity Index (WPAI) questionnaire administered in NHWS was used to estimate productivity loss due to insomnia. A higher WPAI score indicates greater work and activity impairment. Respondents in the UK subset (N=10,408) who reported insomnia symptoms had greater work productivity scores (31.7 [29.9] vs 20.6 [28.9], $p<0.001$) and greater activity impairment scores (35.5 [29.1] vs 20.3 [26.7], $p<0.001$), compared to those who did not, analysis of the WPAI and ISI[®] data demonstrated increasing absenteeism and presenteeism with an increasing ISI[®] score, indicating that more severe insomnia symptoms is associated with greater productivity loss.¹⁶

In the UK, approximately 300,000 patients are on short-term therapies for 12 months or longer.²⁴ Chronic use of hypnotics is associated with somnolence and impaired daytime functioning, further adding to the already substantial impact of chronic insomnia on work productivity.³¹ Due to concerns with chronic use of hypnotics resulting in tolerance or dependence, NICE guidance NG215 states that the duration of therapy should reflect the management plan and comply with guideline recommendations, and recommends prescribers to communicate clearly to patients about the intended duration of therapy and plans for periodic review.³²

Clinical Pathway

Key Facts:

- Many patients initially self-treat using a range of strategies including improved sleep-hygiene, diet, exercise, or over-the-counter medication to manage symptoms – however the benefits of these approaches are often transient. Despite this, many GPs use a similar strategy upon initial diagnosis.²⁴
- After two to five GP consultations, patients who do not experience adequate symptom relief from non-pharmacological therapies are then prescribed pharmacotherapies such as benzodiazepines, Z-drugs, and melatonin.³³ Pharmacotherapies are recommended only for a short duration (<4 weeks, or <13 weeks for melatonin) with the aim of re-establishing natural, subjectively satisfying sleep.^{10,27}
- Hypnotics can effectively treat night-time symptoms of insomnia, however, psychological dependence often leads to the use of these medications beyond the recommended duration, as most patients are willing to trade-off the safety concerns for a good night's sleep.³¹
- The UK GP survey revealed an extremely low referral rate of approximately 1%, suggesting that majority of the patients are managed in primary care. This may be due to under-developed referral pathways and referrals being considered only in cases of other suspected disorders or if the patient is in an occupational at-risk group.³³
- No existing UK guidance includes recommendations for long-term treatment of insomnia disorder – Likely driven by the lack of licensed longer-term treatment options. The NICE Clinical Knowledge Summary (CKS) recommends managing patients with insomnia disorder in primary care unless referral is required due to presence of other sleep disorders, treatment in primary care has failed or the patient has an occupational risk.²⁷

Treatment pathway

Patient journey

The typical journey of an insomnia patient can be described in the following stages:

1. With onset of insomnia symptoms, patients may self-initiate healthy behavioural changes, including sleep hygiene practices, diet and exercise. Additionally, patients may take plant-based products or over-the-counter (OTC) antihistamines based on their own research or under the advice of friends/family or a pharmacist. The benefits of these approaches are often transient.
2. When symptoms are severe enough to affect patients' daily activities, they consult their GPs. A survey conducted in May 2022 among more than 1,000 GPs in the UK reported that they tend to start with non-pharmacological therapies such as sleep hygiene advice, OTC treatment, or face-to-face/ digital CBTi.³³
3. After two to five GP consultations, patients who do not experience adequate symptom relief from non-pharmacological therapies are then prescribed pharmacotherapies such as

benzodiazepines, Z-drugs, or melatonin.³³ Pharmacotherapies are recommended only for a short duration (<4 weeks, or <13 weeks for melatonin) with the aim of re-establishing natural, subjectively satisfying sleep.^{10,27}

4. Hypnotics can effectively treat night-time symptoms of insomnia, however, psychological dependence often leads to the use of these medications beyond the recommended duration, as most patients are willing to trade-off safety concerns in return for a good night's sleep.³¹ Considering insomnia disorder is a pervasive condition with a chronic course, most patients continue short-term treatments for extended periods despite safety concerns such as risk of dependence, next-day residual effects and withdrawal symptoms or rebound upon discontinuation. Insomnia being a refractory condition reoccurring upon treatment discontinuation, GPs tend to continue these treatments to manage patient expectations despite being aware that they are only indicated for short-term use. This is attributed to the lack of access to safe and effective long-term pharmacotherapies.³⁴ Due to the prolonged usage of hypnotics and other medicines associated with dependence or withdrawal symptoms, coupled with the lack of alternative treatment options, NICE recently issued a guidance (NG215) to provide recommendations on safe prescription and withdrawal management of these drugs.³²

The UK GP survey revealed an extremely low referral rate of approximately 1%, suggesting that a majority of UK patients are managed in primary care. While there are specialist sleep centres in the UK, it is important to note these are not for chronic insomnia, and in reality, there are no chronic insomnia services in England. It is likely that referrals are only being considered in cases of other suspected disorders or if the patient is in an occupational at-risk group.³³

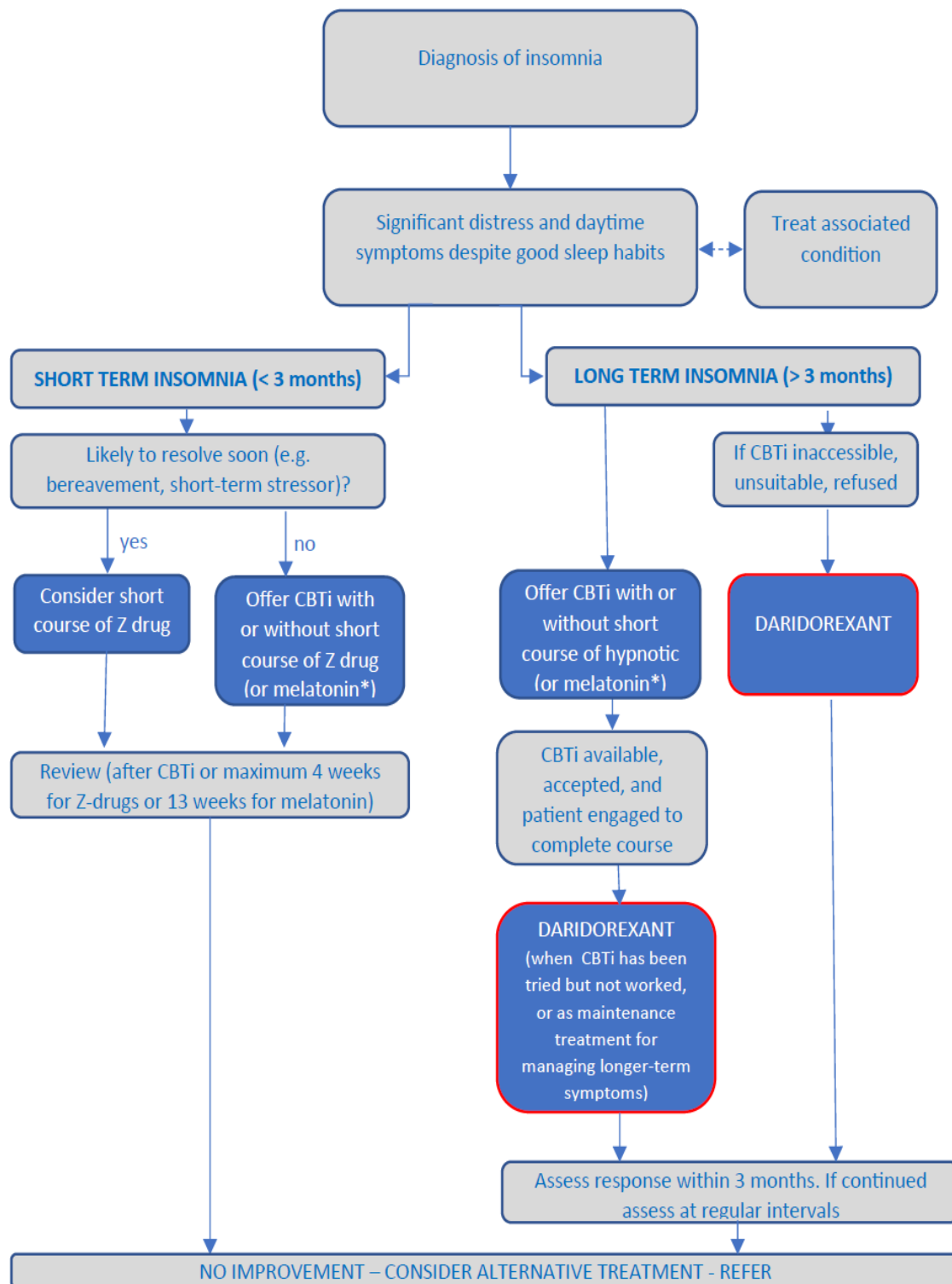
Clinical treatment pathway

Given the chronicity of insomnia disorder, longer-term treatment is anticipated as part of its clinical treatment pathway. However, none of the existing guidelines include recommendations for long-term treatment of insomnia disorder.

The optimal goal of therapy in insomnia disorder is to improve sleep and daytime functioning.^{10,27} The NICE Clinical Knowledge Summary (CKS) recommends managing patients with insomnia disorder in primary care and restricting specialist referral.²⁷ Monitoring response to treatment is an important element in the management of insomnia disorder, partly driven by the safety concerns associated with current pharmacotherapy. The CKS recommends periodic review (i.e., every 2–4 weeks) of insomnia symptoms to evaluate the need to continue treatment.²⁷

The pathway proposed in Figure 1 is based on the 2019 British Association for Psychopharmacology consensus statement and has been updated to reflect the latest daridorexant data, licensed indication, and agreed positioning from NICE during their recent technology appraisal.²

Figure 1 - Proposed pathway update following the availability of daridorexant:



*For people aged 55 or older; *for acute exacerbation of symptoms

The British Association for Psychopharmacology (BAP), the European guideline for the diagnosis and treatment of insomnia, and the NICE Clinical Knowledge Summaries are generally aligned and recommend CBTi as the first-line treatment for insomnia disorder.^{10,27} In May 2022, NICE recommended a digital CBTi option, Sleepio, for treating insomnia and insomnia symptoms in primary care for people who would otherwise be offered sleep hygiene or sleeping pills.³⁵

It is anticipated that CBTi, either digital or face to face, will primarily be used as a first-line therapy for treatment-naïve patients. The use of QUVIVIQ would replace pharmacological therapies in treatment-experienced patients who have already exhausted standard care, after treatment with CBTi, or when a patient is not suitable for CBTi.

A short course of hypnotic-drug treatment is proposed for severe cases that do not respond to non-pharmacotherapy, but only for one week. QUVIVIQ is the first insomnia treatment with longer term data, and it is indicated for the treatment of chronic insomnia without restrictions on treatment duration, though should be reviewed within 3 months.

When CBTi is unavailable, unsuitable, or ineffective, pharmacotherapy is considered. Benzodiazepines and Z-drugs are recommended as hypnotics for chronic insomnia disorder that should be restricted to the shortest possible duration (<4 weeks) due to safety risks of prolonged usage, especially dependency.^{10,27} Note these products are also not licensed for long term use. Prolonged release melatonin is recommended for insomnia disorder patients aged ≥55 years for an initial duration of 3 weeks, which should only be continued for another 10 weeks if an adequate response is achieved.^{10,27}

Apart from daridorexant there are currently no recommended or licensed drug classes indicated for long-term treatment of chronic insomnia.

Available pharmacological treatments for chronic insomnia are usually only considered after non-pharmacological interventions have been tried and not been effective. Current pharmacological treatments lack long term efficacy data and are associated with a number of side effects, including dependency. Despite only being recommended for short-term use, sleep medications are often used off-label long-term.¹⁰

Limitations of current care

Key Facts:

- The non-pharmacological approach of CBTi is the recommended first-line treatment for insomnia disorder, however several issues are likely to limit its consistent effectiveness:
 - poor access and availability of face-to-face CBTi has been a longstanding problem in the UK.^{33,35}
 - Being resource intensive, CBTi is designed to be completed in 6 weeks.³⁶
 - Adherence to CBTi is often poor, with patients having to invest personal time and be disciplined to practise CBTi measures.³⁷
 - the lack of a standardised accredited training for CBTi can lead to inconsistent results.³⁷
 - sleep restriction, a behavioural component of CBTi, is often associated with impaired daytime functioning, interfering with attention and other cognitive processes.^{38,39}
- Pharmacological therapy is considered for treatment naïve patients when CBTi is unavailable, unsuitable or ineffective, but BZ and Z-drugs should be restricted to the shortest possible duration (<4 weeks), in line with their licensed indications and due to safety risks associated with prolonged usage.^{10,23,27}
- Daridorexant is the first DORA to be approved in the UK and Europe for the treatment of insomnia disorder. It is an evidence-based treatment with established efficacy and safety for up to one year.⁴⁴ The clinical trials of daridorexant demonstrated improved night-time and daytime symptoms of insomnia in adult and elderly patients with a favourable safety profile.^{43,44} Upon discontinuation of daridorexant, with up to 12 months of continuous treatment in clinical studies, there was no evidence of abuse, no withdrawal symptoms (indicating no physical dependence), and no sign of rebound insomnia
- The recommended positioning of daridorexant (as agreed with NICE during their 2023 technology assessment) is as a second-line treatment option when digital or face-to-face CBTi has been tried but not worked, or as maintenance treatment for managing longer-term symptoms. Or, as a first-line treatment option when CBTi is not available or unsuitable.

The need for effective treatment:

While CBTi is the recommended first-line treatment for insomnia disorder, poor access and availability of face-to-face CBTi has been a longstanding problem in the UK.³⁵ Being resource intensive, CBTi is administered for a maximum of 6 weeks per patient in the NHS.³⁶ Adherence to CBTi is often poor, with patients having to invest personal time and be disciplined to practise CBTi measures.³⁷ In addition, the lack of a standardised accredited training for CBTi can lead to inconsistent results.³⁷ Although NICE's recommendation of Sleepio® for treating insomnia is likely to significantly improve access and reduce cost of CBTi,³⁵ refusal and failure rates associated with CBTi remain high.³³ In addition, sleep restriction, a behavioural component of CBTi, while being an efficient way of treating insomnia disorder,³⁸ is often associated with impaired daytime functioning, interfering with attention and other cognitive processes.³⁹

Second-line options are also limited. Primary care clinicians are hesitant to prescribe hypnotic treatments, citing safety concerns and poor experience with their use in other patients.²⁴ Consequently, up to 70% of patients in the UK with chronic insomnia are not effectively treated with prescription drugs, further contributing to the burden of this condition.²⁴

Current treatments:

Non-pharmacological treatment

Current guidelines recommend CBTi as the first-line treatment for chronic insomnia.^{10,23,27} Depending on the needs of a patient, CBTi is administered alone or is augmented with short-term pharmacotherapy. CBTi comprises five major components, namely sleep hygiene, sleep education, stimulus control, muscle relaxation, and sleep restriction. It can be delivered by psychologists, primary care practitioners including nurses, or self-administered (e.g., digital applications).^{10,23,27}

Sleepio[®], a self-help digital sleep improvement programme based on CBTi, includes a sleep test, weekly interactive CBTi sessions and regular sleep diary entries. It is designed to be completed in six weeks; however, users have full access to the programme for up to 12 months.³⁵ NICE has recently recommended Sleepio[®] as a cost-saving treatment option for insomnia in primary care for people who would otherwise be offered sleep hygiene or sleeping pills.³⁵ The availability of Sleepio[®] is likely to improve the poor access and availability of CBTi in England.

Pharmacotherapy

Pharmacotherapy is considered for treatment naïve patients when CBTi is unavailable, unsuitable or ineffective. The NICE CKS, BAP and European Sleep Research Society (ESRS) guidelines recommend:^{10,23,27}

- BZs and Z-drugs as hypnotics that should be restricted to the shortest possible duration (<4 weeks) due to safety risks associated with prolonged usage. These safety risks include cognitive impairment, daytime somnolence, tolerance and dependence.⁴⁰ In addition, abrupt discontinuation can lead to rebound insomnia and withdrawal symptoms.⁴¹
- Use of prolonged-release melatonin in patients aged ≥55 years. The recommended initial duration of treatment is 3 weeks. If adequate response is achieved, the treatment should only be continued for another 10 weeks. While melatonin has a better safety profile than BZs and Z-drugs, it is associated with daytime somnolence and should be used with caution in the elderly.²⁷

The ESRS and BAP guidelines recommend intermittent dosing of BZs and Z-drugs to mitigate safety risks. The guidelines also recommend the use of sedating antidepressants for short-term treatment of chronic insomnia.^{10,23} The BAP guidelines do not recommend anti-psychotics as first line pharmacotherapy, while the ESRS guideline recommend against using anti-psychotics for chronic insomnia.^{10,23} Non-selective antihistamines have limited role in the treatment of insomnia disorder due to its lack of evidence.^{10,23}

None of the currently recommended drug classes are licensed for long-term treatment of insomnia disorder due to safety concerns and the risk of developing tolerance and/or dependence. Yet, these drug classes are commonly used 'off-label', i.e. beyond their recommended duration (i.e., <4 weeks for hypnotics, ≤13 weeks for melatonin). A UK insomnia market landscape analysis showed that patients on average were on prescription drugs for 194 days in 2021.²⁴ Specifically, the average duration of therapy was 102 days for zopiclone, 208 days for melatonin and 271 days for amitriptyline.⁴² A survey among UK-based clinicians showed that only 33% perceived current prescription drugs as having a positive impact on insomnia. When asked about the reasons for prescribing these drugs beyond the recommended duration, 78% cited a lack of long-term options as the main reason.³⁴

Daridorexant

Daridorexant is the first dual orexin receptor antagonist (DORA) to be approved in the UK and Europe for the treatment of chronic insomnia. It is an evidence-based treatment with established efficacy and safety for up to one year.^{43,44} The clinical trials of daridorexant demonstrated improved night-time and daytime symptoms of insomnia in adult and elderly patients with a favourable safety profile. Patients who received daridorexant did not experience next-morning residual symptoms or show signs of abuse at the recommended dosages of 25 and 50 mg daily.⁴³ In addition, patients treated with daridorexant did not show any signs of rebound insomnia or withdrawal symptoms upon treatment discontinuation.⁴³

Early treatment with daridorexant can help improve patients' QoL, thereby improving their work productivity,⁴³ and minimising exposure to off-label and potentially harmful pharmacotherapies.

Daridorexant can be prescribed in primary care, providing an efficacious option for patients as a second-line treatment option when digital or face-to-face CBTi has been tried but not worked, or as maintenance treatment for managing longer-term symptoms, or as a first-line treatment option when CBTi is not available or unsuitable.²

Clinical Evidence

Key Facts:

- The results from phase III confirmatory study 301 and extension study 303 demonstrated that treatment with daridorexant 50 mg once daily in patients with insomnia disorder was superior to placebo for the primary efficacy endpoints of objective sleep induction (LPS) and maintenance (WASO), as well as being well tolerated. ^{43,44}
- Superiority over placebo was also demonstrated for key secondary subjective endpoints of patient reported sleep quantity (sTST) and daytime functioning (IDSIQ scores). ⁴³
- The benefits of daridorexant on patient-reported sleep quantity and daytime functioning were sustained for up to a year, as shown by the improved sTST and IDSIQ sleepiness domain score at month 6, month 9 and month 12. ^{43,44}
- Treatment with daridorexant 50 mg once daily led to a clinically and statistically significant change from baseline in WASO by 22.8 minutes and LPS by 11.4 minutes at month 1 compared with placebo. The results met the pre-specified effect size of 0.37, which is comparable with those of other pharmacotherapies for insomnia disorder. The reductions were consistent throughout the 301 study, with daridorexant 50 mg significantly reducing (from baseline): WASO by 18.3 minutes and LPS by 11.7 minutes at month 3 compared with placebo. ⁴³ Symptom improvement was achieved despite placebo treatment being well documented as a driver of improvement in insomnia trials. ⁴
- Treatment with daridorexant 50 mg once daily demonstrated statistically significant improvements in patient-reported sTST and IDSIQ sleepiness domain score. Self-reported TST improved by 22.1 minutes and 19.8 minutes at month 1 and month 3, respectively compared with placebo. Similarly, IDSIQ sleepiness domain score reduced by 1.75 and 1.90 points at month 1 and month 3, respectively compared with placebo. ⁴³
- The results of extension study 303 showed that the effects of daridorexant on patient-reported sleep quantity and quality were sustained for up to a year on treatment. Compared with placebo, daridorexant 50 mg once daily led to improvement in sTST of 20.4 minutes at month 6, but minor improvement of 15.8 minutes and 17.8 minutes at month 9 and month 12, respectively. IDSIQ sleepiness domain scores improved across all timepoints among patients treated with daridorexant compared to those treated with placebo. ⁴⁴
- Daridorexant was well tolerated in both adult and elderly patients. In confirmatory study 301, the incidence of somnolence was low among subjects in the daridorexant 50 mg group and was numerically lower than that in the placebo group. Nausea, headaches, mild dizziness, and fatigue were slightly more frequent in the daridorexant group than placebo group, whereas the incidence of falls was slightly lower in the daridorexant group than placebo group. These findings were consistent with those of extension study 303. In both studies, daridorexant demonstrated no next-morning residual effects, no evidence of abuse potential, and no signs of rebound insomnia or withdrawal symptoms upon treatment discontinuation. ^{43,44}
- A major challenge in patients with insomnia disorder is to reverse impaired daytime functioning. Subjects in the daridorexant 50 mg group reported improvements in all aspects of daytime functioning compared to placebo in both confirmatory study 301 and extension study 303, as assessed by IDSIQ total score, mood domain score, alert/cognition domain score, and sleepiness domain score. The ability to reverse impaired daytime functioning demonstrated by daridorexant addresses an important gap in the current insomnia disorder treatment landscape. ^{43,44}

Clinical Trial Programme:

Daridorexant has been studied in five clinical trials, as described in Table 1. This document will focus on the 301 and 303 studies, which deliver critical data describing the recommended 50mg once-daily dose, for formulary application. Study 301 (25mg, 50mg) and 302 (25mg, 10mg) were the pivotal phase-3 studies, and 303 (10mg, 25mg, 50mg) was the extension study. Full details of all studies is available upon request from Manisha.oberoi@idorsia.com

Table 1 - Daridorexant clinical trial program

Study name	Study identifier	Main objective	Status
201	NCT02839200	Assess the efficacy and safety of daridorexant in adult subjects with insomnia disorder (dose response study)	Completed
202	NCT02841709	Assess the efficacy and safety of daridorexant in elderly subjects with insomnia disorder	Completed
301	NCT03545191	Assess the efficacy and safety of daridorexant in adult and elderly subjects with insomnia disorder	Completed
302	NCT03575104	Assess the efficacy and safety of daridorexant in adult and elderly subjects with insomnia disorder	Completed
303	NCT03679884	Assess the long-term safety and tolerability of daridorexant in adult and elderly subjects with insomnia disorder	Completed

Study 301: Design

Study 301 was a multi-centre, randomized, double-blind, placebo-controlled, parallel-group phase III study evaluating two different doses (25 mg and 50 mg) of daridorexant versus placebo for 3 months (84 ± 2 days), conducted in 75 sites across 10 countries (Australia, Canada, Denmark, Germany, Italy, Poland, Serbia, Spain, Switzerland, and the US).⁴³

Table 2 - Study 301 Design

Study 301 - ID-078A301 (NCT03545191)	
Study Design	A multi-centre, randomized, double-blind, placebo-controlled, parallel-group phase III study evaluating two different doses (25 mg and 50 mg) of daridorexant for 3 months (84 ± 2 days). 310 subjects were enrolled in each of the Daridorexant 25mg, 50mg and placebo arms
Population	Adult (18-64 years) and elderly (≥ 65 years) male and female subjects with a diagnosis insomnia disorder as per the DSM-5 [®] criteria and moderate-to-severe insomnia as per ISI [®] ($ISI^{\circ} \geq 15$).
Study treatments	Subjects were randomized in a 1:1:1 ratio to either dose of • Daridorexant 25mg • Daridorexant 50mg • Placebo All taken as one tablet taken orally once daily in the evening

Key eligibility criteria	Screening phase: from signing informed consent at Visit 1 until randomization (Visit 4), lasting 20 to 31 days. Eligibility for the study was assessed at multiple time points during the screening phase, according to the inclusion and exclusion criteria. Inclusion: • Insomnia disorder according to the DSM-5[®] criteria. • Self-reported insomnia of at least moderate severity (ISI[®] score ≥ 15) at screening. • Sleep disturbance causing clinically significant distress or impairment in social, occupational, educational, academic, behavioural, or other important functioning. • Self-reported insufficient sleep quantity (≥ 30 minutes to fall asleep, wake time during sleep ≥ 30 minutes, and $sTST \leq 6.5$ hours during the night) for at least 3 nights per week during at least 3 months prior to the screening visit, and for at least 3 out of 7 nights on the SDQ completed during the placebo run-in period prior to the run-in PSG nights. • Objective sleep quantity parameters assessed on 2 consecutive PSG nights during the placebo run-in period: mean LPS ≥ 20 minutes, with neither of the 2 nights < 15 minutes; mean WASO ≥ 30 minutes, with neither of the 2 nights < 20 minutes; and mean TST < 420 minutes. • Subjects were required to sign informed consent prior to any procedure. Exclusion • Subjects self-reporting daytime napping ≥ 1 hour per day and ≥ 3 days per week. • Subjects with BMI < 18.5 or > 40.0 kg/m². • Subjects who were pregnant, breastfeeding, or planning to become pregnant. • Subjects with any lifetime history of suicide attempt, sleep-related breathing disorders, periodic limb movement disorder, restless legs syndrome, circadian rhythm disorder, REM behaviour disorder, narcolepsy, or apnoea/hypopnea. • Subjects with acute or unstable psychiatric conditions, suicidal ideation with intent, alcohol or drug abuse, or with history or clinical evidence of any disease, medical condition or treatment that could affect the subject's safety or interfere with the study assessments. • Subjects aged ≥ 50 years with a Mini Mental State Examination[®] score < 25.
Primary outcome	• Change from baseline^a to month 1^b and 3^b in WASO ◦ WASO was the time spent awake after onset of persistent sleep (beginning of the first continuous 20 epochs [i.e., 10 min] scored as non-awake, i.e., epochs scored as either S1, S2, SWS or REM until lights on, as determined by polysomnography (PSG). • Change from baseline^a to month 1^b and 3^b in LPS ◦ LPS was the time from start of recording to the beginning of the first continuous 20 epochs (i.e., 10 min) scored as non-awake, i.e., epochs scored as either S1, S2, SWS or REM, as determined by PSG.
Key secondary outcomes	• Change from baseline^c to month 1^d and 3^d in $sTST$ • Change from baseline^c to month 1^d and 3^d in IDSIQ sleepiness domain score

Other efficacy endpoints	• Change from baseline^a to month 1^b and 3^b in TST • Change from baseline^c to month 1^d and 3^d in sWASO • Change from baseline^c to month 1^d and 3^d in sLSO • Change from baseline^c to month 1^d and 3^d in IDSIQ scores
Key Safety Endpoints	• TEAEs up to 30 days after double-blind study treatment discontinuation or until enrolment into study 303 • SAEs up to 30 days after double-blind study treatment discontinuation or until enrolment into study 303 • AEs leading to premature discontinuation of treatment • AESI after adjudication by the ISB (narcolepsy-like symptoms or suicide/self-injury) • Withdrawal effects (physical dependence) upon treatment discontinuation • Changes from baseline to Month 1 and Month 3 in SDS© [questionnaire on impairment of work, social life, and family life/home responsibilities, each on a 10-point scale]

^aBaseline: mean of the 2 PSG nights at Visit 3.

^bMonth 1 and Month 3: mean of the 2 PSG nights at Visit 6 and Visit 8, respectively

^cBaseline: mean value based on the screening SDQ/IDSIQ entries performed at home in the 7 days immediately preceding the first PSG at Visit 3.

^dMonth 1 and Month 3: mean value based on the SDQ/IDSIQ entries performed at home in the 7 days immediately preceding the first PSG at Visit 6 and Visit 8, respectively.

Study 301: Results

Primary efficacy endpoint results:

Primary efficacy results from the 301 Study are described below in Table 3 and Table 4. WASO was significantly reduced from baseline among subjects in the daridorexant 50 mg group compared to subjects in the placebo group at month 1 (LSM difference -22.78 minutes [min], [95% CI -28.00 to -17.57], $p < 0.0001$) and month 3 (LSM difference -18.30 min, [-23.95 to -12.66], $p < 0.0001$).⁴³

Similarly, LPS showed a significant reduction from baseline among subjects in the daridorexant 50 mg group compared to subjects in the placebo group at month 1 (LSM difference -11.35 min, [-16.02 to -6.69], $p < 0.0001$) and month 3 (LSM difference -11.67 min, [-16.35 to -6.99], $p < 0.0001$).⁴³

Table 3 - Between treatment analysis for change from baseline in WASO (min) to Month 1 and Month 3 Full Analysis Set. 43

					Difference to placebo			
	n	LSM	SE	95% CL	LSM	SE	95% CL	p-value (two-sided)
<i>Change from baseline to Month 1</i>								
Daridorexant 50 mg	305	-28.98	1.877	[-32.668, -25.299]	-22.78	2.657	[-27.996, -17.567]	<.0001
Placebo	299	-6.20	1.899	[-9.928, -2.475]				
<i>Change from baseline to Month 3</i>								
Daridorexant 50 mg	287	-29.41	2.031	[-33.399, -25.427]	-18.30	2.875		<.0001

Placebo	283	-11.11	2.049	[-15.131, -7.088]	[-23.945, -12.661]
---------	-----	--------	-------	-------------------	--------------------

Daridorexant (n=310), Placebo (n=310)

Table 4 - Between treatment analysis for change from baseline in LPS (min) to Month 1 and Month 3 Full Analysis Set. 43

					Difference to placebo			p-value (two-sided)
	n	LSM	SE	95% CL	LSM	SE	95% CL	
<i>Change from baseline to Month 1</i>								
Daridorexant 50 mg	305	-31.20	1.684	[-34.506, -27.896]	-11.35	2.378	[-16.022, -6.687]	<.0001
Placebo	299	-19.85	1.697	[-23.177, -16.515]				
<i>Change from baseline to Month 3</i>								
Daridorexant 50 mg	287	-34.80	1.689	[-38.118, -31.490]	-11.67	2.383	[-16.348, -6.994]	<.0001
Placebo	283	-23.13	1.697	[-26.464, -19.803]				

Daridorexant (n=310), Placebo (n=310)

Secondary efficacy endpoint results:

Key secondary efficacy results from the 301 Study are described below in Table 5 and Table 6. Compared with placebo, sTST significantly increased from baseline in the daridorexant 50 mg group at month 1 (LSM difference 22.06 min, [14.405 to 29.708], $p < 0.0001$) and month 3 (LSM difference 19.77 min, [10.623 to 28.918], $p < 0.0001$).⁴³

Subjects in the daridorexant 50 mg group reported significant reduction from baseline in IDSIQ sleepiness domain score compared to placebo at month 1 (LSM difference -1.75, [-2.51 to -0.98], $p < 0.0001$) and month 3 (LSM difference -1.90, [-2.95 to -0.98], $p = 0.0002$).⁴³

Table 5 - Between treatment analysis for change from baseline in sTST (min) to Month 1 & Month 3. 43

					Difference to placebo			p-value (two-sided)
	n	LSM	SE	95% CL	LSM	SE	95% CL	
<i>Change from baseline to Month 1</i>								
Daridorexant 50 mg	304	43.62	2.774	[38.173, 49.063]	22.06	3.899	[14.405, 29.708]	<.0001
Placebo	302	21.56	2.782	[16.101, 27.022]				
<i>Change from baseline to Month 3</i>								
Daridorexant 50 mg	289	57.67	3.311	[51.171, 64.168]	19.77	4.661	[10.623, 28.918]	<.0001
Placebo	289	37.90	3.315	[31.393, 44.404]				

Daridorexant (n=310), Placebo (n=310)

Table 6 - Between treatment analysis for change from baseline IDSIQ sleepiness domain score to Month 1 & Month 3. 43

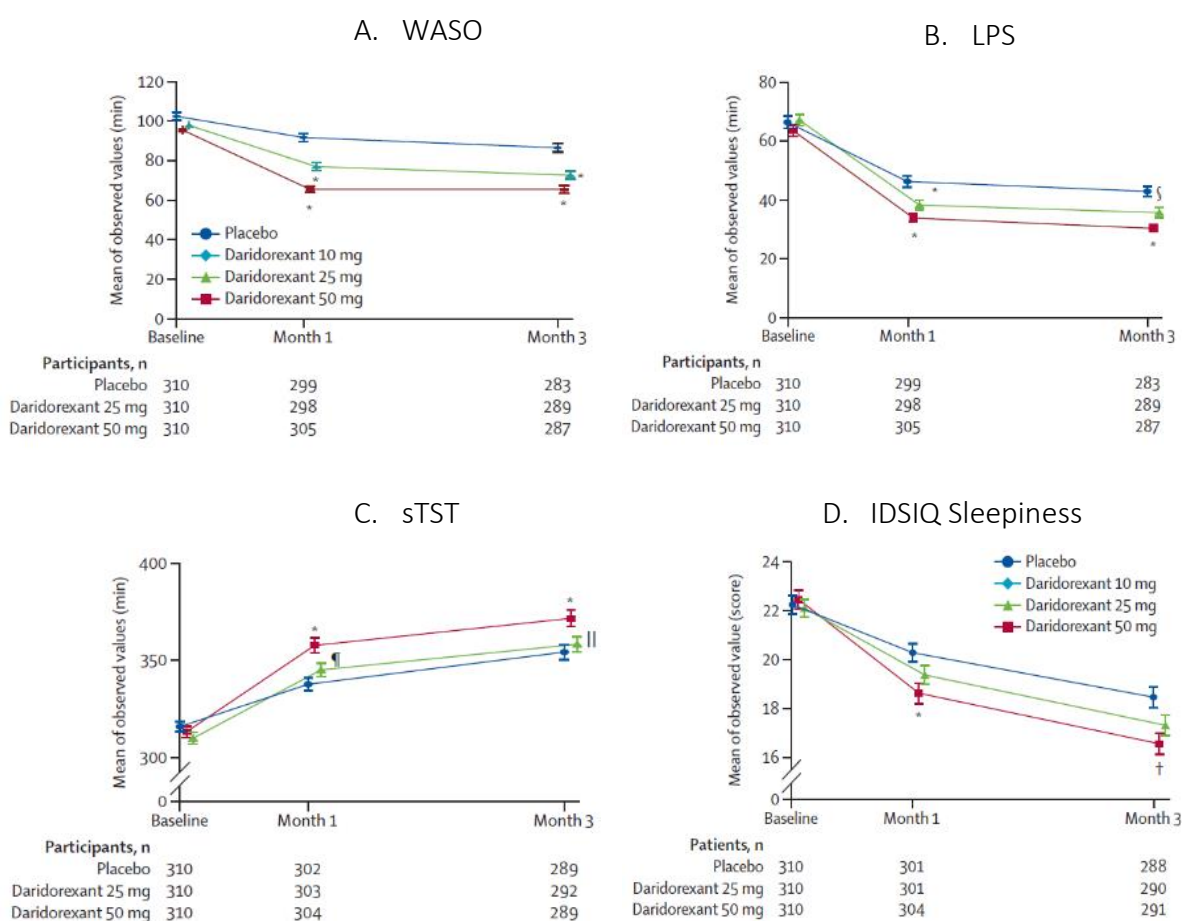
					Difference to placebo			
	n	LSM	SE	95% CL	LSM	SE	95% CL	p-value (two-sided)
Change from baseline to Month 1								
Daridorexant 50 mg	304	-3.77	0.276	[-4.309, -3.224]	-1.75	0.389	[-2.508, -0.983]	<.0001
Placebo	301	-2.02	0.278	[-2.566, -1.476]				
Change from baseline to Month 3								
Daridorexant 50 mg	291	-5.70	0.361	[-6.405, -4.987]	-1.90	0.510	[-2.905, -0.905]	0.0002
Placebo	288	-3.79	0.363	[-4.503, -3.080]				

Daridorexant (n=310), Placebo (n=310)

Study 301: Efficacy Summary

Night-time efficacy endpoints and IDSIQ sleepiness domain scores are represented below in Figure 2.

Figure 2 - Night-time efficacy endpoints and IDSIQ sleepiness domain scores. 43



Subgroup analyses of primary and secondary efficacy endpoints

Subgroup analysis was performed to evaluate the consistency of treatment effect across the following demographic subgroups:

- Age: < 65, ≥ 65 years
- Sex: Male, female
- Region: US, other (non-US)

The effect of daridorexant 50mg on the primary and key secondary efficacy endpoints was consistent in adults and elderly and across sex and geographical location.⁴³

Study 301: Safety

Treatment emergent adverse events (TEAEs)

During the double-blind study period, 37.7% and 34.0% of subjects reported TEAEs in the daridorexant 50 mg group, and placebo group, respectively. Most of the events were of mild or moderate intensity. Nasopharyngitis [6.5% (daridorexant 50 mg); 6.5% (placebo)] and headache [6.2% (daridorexant 50 mg); 3.9% (placebo)] were the most commonly reported TEAEs; followed by accidental overdose (2.6% vs 1.6%), fatigue (2.3% vs 0.6%), dizziness (2.3% vs 0.6%), and nausea (2.3% vs 1.0%).⁴³

TEAEs that occurred during the double-blind study period considered related to study treatment were reported for 38 (12.3%), and 29 (9.4%) subjects in the daridorexant 50 mg, and placebo groups, respectively. Fatigue was the most frequent TEAE considered related to study treatment in (1.9% in daridorexant 50 mg vs 0.3% in placebo).⁴³

Of note, falls were reported more frequently for placebo (8 subjects) than daridorexant 50 mg group. No suicidal ideation was reported in either treatment groups throughout the entire duration of the study 301.⁴³ Note that across all studies there were 4 reported cases of suicidal ideation, equally distributed across treatment groups including placebo (Study 302, 2 cases, 25mg & 10mg; Study 303, 2 cases, 50mg & placebo). The SPC reminds prescribers that as with other hypnotics, daridorexant should be administered with caution in patients exhibiting symptoms of depression.

Table 7 - TEAEs during the double-blind study period reported for ≥2% in any treatment group.⁴³

Treatment-emergent adverse event	Daridorexant 50 mg N = 308 n (%)	Placebo N = 309 n (%)
Subjects with at least one event	116 (37.7)	105 (34.0)
Nasopharyngitis	20 (6.5)	20 (6.5)
Headache	19 (6.2)	12 (3.9)
Accidental overdose	8 (2.6)	5 (1.6)
Fatigue	7 (2.3)	2 (0.6)
Dizziness	7 (2.3)	2 (0.6)
Nausea	7 (2.3)	3 (1.0)

**Total number of subjects per treatment group with at least one event. Table is truncated to show only those AEs reported for at least 2% in any treatment group. Percentages are based on the treatment group N; n = number of subjects with at least one row event; Subjects may be counted in more than one row. Includes TEAEs occurring (i.e., that started or worsened) during the double-blind study period.*

The incidence of treatment-emergent SAEs was low and were reported in 10 subjects: 3 (1.0%) and 7 (2.3%) subjects in the daridorexant 50 mg and placebo group, respectively. ⁴³

Study 303: Design

Study 303 was a multi-centre, double-blind, parallel-group, randomised, placebo- controlled, extension of confirmatory studies 301 and 302. Subjects who completed double-blind study treatment and the placebo run-out period of the confirmatory studies 301 and 302, and who were willing to participate, were eligible to enrol into study 303. Subjects assigned to a daridorexant group in study 301 or 302 were assigned to the same daridorexant dose (i.e., 10mg, 25mg or 50mg). Subjects assigned to the placebo group in studies 301 or 302 were re-randomized to receive either placebo or daridorexant 25 mg in a 1:1 ratio in study 303. ⁴⁴

Study 303 was conducted in 94 sites across 14 countries (Belgium, Bulgaria, Canada, Denmark, Finland, France, Germany, Hungary, South Korea, Poland, Spain, Sweden, Switzerland, and the US).⁴⁴

Study 303 (NCT03679884)

Study Design	Study 303 was a multi-centre, double-blind, parallel-group, randomised, placebo-controlled, extension of confirmatory studies 301 and 302, comparing daridorexant 10mg, 25mg and 50mg versus placebo over a period of 280 days (+/- 7 days)
Population	In-line with Study 301 and 302
Study treatments	• Daridorexant 10mg • Daridorexant 25mg • Daridorexant 50mg • Placebo All taken as one tablet taken orally once daily in the evening
Key eligibility criteria	Inclusion: • Signed informed consent prior to any study-mandated procedure (Visit 1). • Completion of the double-blind study treatment and placebo run-out period of 301 or 302 (Visit 1). • For woman of childbearing potential, the following was required: • Negative urine pregnancy test (EOT of 301 or 302 studies). • Agreement to use the contraception scheme as required by the protocol from Visit 1 up to at least 30 days after EODBT. Exclusion • Subjects self-reporting daytime napping ≥ 1 hour per day and ≥ 3 days per week. • Subjects with BMI < 18.5 or > 40.0 kg/m². • Subjects who were pregnant, breastfeeding, or planning to become pregnant. • Subjects with any lifetime history of suicide attempt, sleep-related breathing disorders, periodic limb movement disorder, restless legs syndrome, circadian rhythm disorder, REM behaviour disorder, narcolepsy, or apnoea/hypopnea.

	- Subjects with acute or unstable psychiatric conditions, suicidal ideation with intent, alcohol or drug abuse, or with history or clinical evidence of any disease, medical condition or treatment that could affect the subject's safety or interfere with the study assessments. - Subjects aged ≥ 50 years with a Mini Mental State Examination© score < 25. - Subjects treated with central nervous system-active drugs; cognitive behavioural therapy was allowed if started at least 1 month prior to the run-in PSG nights and intended to be continued throughout the study. - Subjects not able or willing to stop treatment with moderate or strong CYP3A4 inhibitors or inducers within at least 1 week prior to the start of the placebo run-in period.
Primary outcomes (safety)	- TEAEs up to 30 days after double-blind study treatment discontinuation. - SAEs up to 30 days after study double-blind treatment discontinuation. - AEs leading to premature discontinuation of the double-blind study treatment. - AESIs after adjudication by ISB: - Narcolepsy-like symptoms (i.e., EDS, cataplexy and complex sleep behaviour events including hallucinations/sleep paralysis) - Suicide/self-injury. - Withdrawal effects (physical dependence) upon treatment discontinuation, assessed based on the changes from last assessment on double-blind treatment (Visit 5, Week 40) to end of the placebo run-out period (Visit 6, Week 41) in the benzodiazepine withdrawal symptom questionnaire (BWSQ) total score, the occurrence of relevant AEs and marked ECG abnormalities. - Change from baseline to Visit 3 (Week 14), Visit 4 (Week 27), and Visit 5 (Week 40) in SDS©.

Study 303: Results

Safety: Treatment emergent adverse events (TEAEs)

During the double-blind study period, 38.0% and 33.6% of subjects reported TEAEs in the daridorexant 50 mg and placebo groups, respectively. Most of the events were of mild or moderate intensity. Nasopharyngitis [8.0% (daridorexant 50 mg); 4.7% (placebo)] was the most commonly reported TEAE. ⁴⁴ Additional TEAEs with an incidence of $\geq 2\%$ in both daridorexant 50mg and placebo groups were accidental overdose (2.9% vs 0%), somnolence (2.9% vs 0%), cough (2.2% vs 0%) and pneumonia (2.2% vs 0%).⁴⁴

Table 8 - TEAEs during the double-blind study period reported for $\geq 2\%$ of subjects in either treatment group*.⁴⁴

Treatment-emergent adverse event	Daridorexant 50 mg N = 137 [n (%)]	Placebo N = 128 [n (%)]
Subjects with at least one event**	52 (38.0)	43 (33.6)
Nasopharyngitis	11 (8.0)	6 (4.7)
Accidental overdose	4 (2.9)	0
Somnolence	4 (2.9)	0
Fall	3 (2.2)	2 (1.6)
Headache	3 (2.2)	2 (1.6)

Cough	3 (2.2)	0
Pneumonia	3 (2.2)	0

**Includes only those TEAEs occurring (i.e., that started or worsened) during the double-blind study period.*

Subgroup analyses was performed to evaluate treatment safety across the following demographic subgroups:

- Age: < 65, ≥ 65 years and <75, ≥75 years
- Sex: Male, female
- BMI: < 25, 25–30, > 30 kg/m²
- Race: White, Black or African American, Other

There were no clinically relevant differences between the two treatment groups in the overall incidence of TEAEs by age, sex, BMI or race. ⁴⁴

The incidence of treatment-emergent SAEs was low (5.1% subjects in the daridorexant 50 mg group vs 1.6% subjects in the placebo group). ⁴⁴

Conclusion

The benefits of daridorexant have been demonstrated in both adults and elderly and across a range of insomnia severity. In conclusion, daridorexant is associated with clinically meaningful improvements in objective sleep onset and maintenance, and subjective sleep quantity and quality as well as daytime functioning. ^{43,44} Daridorexant is the first DORA in the European countries demonstrating safety and efficacy for up to one year, with no next-morning residual effects and no risk of rebound insomnia or withdrawal symptoms upon treatment discontinuation. ⁴⁴ Thus, its recommendation for the treatment of chronic insomnia in primary care will improve outcomes, increase work productivity, and benefit the patient population treated by the NHS.

Economic Impact

Eligible population

The population eligible for daridorexant can be described as adults aged 18 and over, with diagnosed chronic insomnia disorder (defined as per the DSM-5 criteria) and having received prior pharmacotherapy.

In Table 9 we present three scenarios describing the adult population of the UK (52,890,044), the adult population of England (44,456,850), and an ICS population of 100,000 adult residents.

Applying the National Health and Wellness Survey prevalence estimate of 7.3% of patients fulfilling the DSM-5 criteria,¹⁶ approximately 3,860,973 patients with chronic insomnia reside in the UK, 3,245,350 in England, and 7,300 in an example ICS population.

The UK volume pharmacological treatments used for insomnia was estimated using the IQVIA MIDAS database.⁴⁵ In 2021, the annual insomnia market volume was 454,471,000 standard units which can be divided by the mean duration of treatment (194 days) to give an estimate of 2,342,634 individuals in the UK treated with insomnia pharmacological treatment.

Of these, 51% are estimated to have received prior pharmacotherapy, based on the United Kingdom respondents to the NHWS survey who matched the DSM-5 criteria. As such, the proportion of UK adults with DSM-5 insomnia and taking a pharmacological treatment, is estimated at 1,194,743 patients in the UK, 1,004,244 patients in England, and 2,259 patients in the example ICS population.

Table 9 - daridorexant eligible population

	UK	England	ICS example	Reference
Population of adults aged 18+				
	52,890,044	44,456,850	100,000	ONS mid year 2020 ⁴⁶
Proportion fulfilling DSM-5 criteria = 7.3%				
	3,860,973	3,245,350	7,300	NHWS 2020 ¹⁶
Known UK recipients of pharmacological treatment = 2,342,634				
	2,342,634	1,969,106	4,429	IMS ⁴⁵
Proportion receiving pharmacological treatment = 51%				
	1,194,743	1,004,244	2,259	NHWS 2020 ¹⁶

Treatment costs

Table 10 describes the expected costs of introducing daridorexant treatment to an example ICS population of 100,000 residents. Uptake has been estimated based on the sales seen for Circadin following its UK approval, with use increasing from 2.1% in year one, to 11.7% in year five. Daridorexant costs are based on a list price of £1.40 per day and a treatment duration of 194 days based on the 301 trial.

In year one, treatment of 47 eligible patients is expected to cost £12,765, rising to £71,702 in year five when 264 eligible patients are expected to receive treatment.

Table 10 - Budget Impact Estimate

	Year 1	Year 2	Year 3	Year 4	Year 5	Reference
People eligible for treatment with daridorexant (<i>18+, DSM-5, and currently receiving pharmacotherapy</i>)						
	2,259	2,259	2,259	2,259	2,259	Continued from table 9
Projected market share						
	2.1%	4.1%	6.4%	9.0%	11.7%	IMS ⁴⁵
Patient number expected to receive daridorexant						
	47	93	145	203	264	calculated
Annual cost per patient (based on a treatment duration of 194 days)						
	£271.60					List price @ £1.40/day
	£12,765	£25,259	£39,382	£55,135	£71,702	

Potential savings

For simplicity, and to present a conservative budget impact scenario, savings arising from the introduction of daridorexant are not quantified in this document. However, the costs presented above in Table 10 are likely to be an over-estimate based on the following:

- 1) The cost of displaced medicines (including Z-drugs, benzodiazepines, or melatonin) may be realised where clinicians have been using these treatment options off-label, to manage longer term insomnia symptoms. Furthermore the likely resource consumption associated with dependence and withdrawal.
- 2) A reduction in the costs associated with GP, hospital or A+E visits may be realised, if daridorexant moves patients to lower categories of insomnia severity (based on the NHWS survey responses for resource consumption associated with different severities of insomnia)
- 3) Indirect costs associated with absenteeism or presenteeism may be realised, if daridorexant moves patients to lower categories of insomnia severity (based on the NHWS survey responses for absenteeism and presenteeism associated with different severities of insomnia)

Details of the potential direct and indirect cost savings are given in Table 11 and Table 12

Table 11 - Potential direct cost savings¹⁶

	No clinically significant insomnia (0< ISI <7)		Subthreshold insomnia (8< ISI <14)		Clinical insomnia (moderate) (15< ISI <21)		Clinical insomnia (severe) (22< ISI <28)		
Change in Proportion of Patients in ISI Categories from Baseline in Daridorexant 50 mg Compared to Control (at 3 month)									
	4.2%		8.7%		-4.2%		-8.7%		
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	p-value
Number of traditional healthcare provider (GPs and other specialists) visits in past 6 months									
	5.74	0.43	7.33	0.26	7.66	0.29	8.55	0.64	0.002
GP visit cost	£39.23								
How many times have you been to the emergency room for your own medical condition in the past six months?									
	0.29	0.06	0.32	0.03	0.39	0.04	0.41	0.08	0.379
A+E visit cost	£184.62								
How many times have you been hospitalized for your own medical condition in the past six months?									
	0.15	0.04	0.18	0.02	0.21	0.03	0.20	0.05	0.641
Hospitalisation cost	£996.29								

Table 12 - Potential indirect cost savings¹⁶

	No clinically significant insomnia (0< ISI <7)		Subthreshold insomnia (8< ISI <14)		Clinical insomnia (moderate) (15< ISI <21)		Clinical insomnia (severe) (22< ISI <28)		p-value
Change in Proportion of Patients in ISI Categories from Baseline in Daridorexant 50 mg Compared to Control (at 3 month)									
	4.2%		8.7%		-4.2%		-8.7%		
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	p-value
Absenteeism (%)	5.62	1.21	12.35	1.14	17.03	1.71	23.35	5.08	<0.001
Absenteeism may cost £6,493 (based on a mean wage of £13.68/hour, working 7.5 hours/day for 21.25 days/month, for 3 months)									
Presenteeism (%)	16.55	1.40	29.44	1.17	37.12	1.65	41.17	4.06	<0.001
Presenteeism may cost £3,246 (based on a mean wage of £13.68/hour, working 7.5 hours/day for 21.25 days/month, for 3 months at 50% capacity)									

Cost-effectiveness

The cost-effectiveness estimates submitted to NICE, demonstrate that treatment with daridorexant delivers an ICER of between £20,000 and £30,000 per QALY gained over a modelled 12-month period.²

References

- ¹ Idorsia (2022) Summary of Product Characteristics
- ² NICE (2022) [1 \(nice.org.uk\)](https://www.nice.org.uk) Note this refers to Final Draft Guidance. Will be updated when final guidance published.
- ³ RAND 2022 The societal and economic burden of insomnia in adults – an international study – available from www.rand.org/t/RR2166-1 accessed Feb 2023
- ⁴ Bingham Jang et al (2020) Dynamic features of placebo effects addressing persistent insomnia disorder: A meta-analysis of placebo-controlled randomized clinical trials, *Journal of Sleep Research*, v29:4, Available from: <https://onlinelibrary.wiley.com/doi/abs/10.1111/jsr.12997#:~:text=The%20placebo%20effects%20were%20significant,between%20subjective%20and%20objective%20measures>.
- ⁵ Roniger et al (2012) Cognitive behavioral therapy for insomnia helps to reverse cognitive impairment in insomnia patients. *Sleep Sci.* 2022;15(Special 2):355-360
- ⁶ MHRA (2022) Public Assessment Report: QUVIVIQ™. Available from <https://mhraproducts4853.blob.core.windows.net/docs/ed2aeb19a5f58327b069031bc07c8f3a3ad2dec2> accessed Feb 2023
- ⁷ European Medicines Agency (2022), Assessment Report, available from: https://www.ema.europa.eu/en/documents/assessment-report/quvivig-epar-public-assessment-report_en.pdf
- ⁸ Ishak WW, Bagot K, Thomas S, Magakian N, Bedwani D, Larson D, et al. Quality of life in patients suffering from insomnia. *Innov Clin Neurosci.* 2012;9(10):13-26.
- ⁹ Yin J, Jin X, Shan Z, Li S, Huang H, Li P, et al. Relationship of Sleep Duration With All-Cause Mortality and Cardiovascular Events: A Systematic Review and Dose-Response Meta-Analysis of Prospective Cohort Studies. *Journal of the American Heart Association.* 2017;6(9):e005947.
- ¹⁰ Wilson S, Anderson K, Baldwin D, Dijk DJ, Espie A, Espie C, et al. British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders: An update. *J Psychopharmacol.* 2019;33(8):923-47.
- ¹¹ DSM-5 (Diagnostic and statistical manual of mental health disorders – fifth edition) 2013, American Psychiatric Association.
- ¹² Sateia MJ. International Classification of Sleep Disorders-Third Edition. *CHEST.* 2014;146(5):1387-94.
- ¹³ Substance Abuse and Mental Health Services Administration. Table 3.36, DSM-IV to DSM-5 Insomnia Disorder Comparison. CBHSQ Methodology Report. Center for Behavioral Health Statistics and Quality. Substance Abuse and Mental Health Services Administration Substance Abuse and Mental Health Services Administration, Rockville, MD.; 2016
- ¹⁴ Data on file. Real World Evidence of Burden of Illness for Insomnia in Europe (EUR5: France, Germany, United Kingdom, Italy and Spain), the United States, and Japan.
- ¹⁵ National Health and Wellness Survey (NHWS): Cerner Enviza; [Available from: <https://www.cernerenviza.com/real-world-data/national-health-and-wellness-survey-nhws>] Accessed on May 2022.
- ¹⁶ Idorsia Pharmaceuticals Ltd. Data on File. BV_Insomnia-NHWS Results_UK_v1.0_23March2021. . Cerner Enviza2021.
- ¹⁷ Cormier R. Sleep Disturbances. In: Walker HK HW, Hurst JW, editor. *Clinical Methods: The History, Physical, and Laboratory Examinations* 3rd edition. Boston: Butterworths 1990.
- ¹⁸ ICD-11 for Mortality and Morbidity Statistics (Version : 02/2022). Insomnia disorders. 2022 [Available from: <https://icd.who.int/browse11/l-m/en#/http://id.who.int/icd/entity/1038292737>] Accessed on May 2022.
- ¹⁹ Andrew D. Krystal; Ruth M. Benca; and Thomas S. Kilduff. Understanding the Sleep-Wake Cycle: Sleep, Insomnia, and the Orexin System. *J Clin Psychiatry.* 2013;74(suppl 1):3-20.
- ²⁰ Gagnon C, Bélanger L, Ivers H, Morin CM. Validation of the Insomnia Severity Index in primary care. *J Am Board Fam Med.* 2013;26(6):701-10.
- ²¹ Rosekind MR, Gregory KB. Insomnia risks and costs: health, safety, and quality of life. *Am J Manag Care.* 2010;16(8):617-26.
- ²² Winkelmann JW. Insomnia Disorder. *N Engl J Med.* 2015;373(15):1437-44.
- ²³ Riemann D, Baglioni C, Bassetti C, Bjorvatn B, Dolenc Groselj L, Ellis JG, et al. European guideline for the diagnosis and treatment of insomnia. *J Sleep Res.* 2017;26(6):675-700.
- ²⁴ Data on file. UK Insights Deep Dive. 2022.

- ²⁵ Li L, Gan Y, Zhou X, Jiang H, Zhao Y, Tian Q, et al. Insomnia and the risk of hypertension: A meta-analysis of prospective cohort studies. *Sleep Med Rev.* 2021;56:101403.
- ²⁶ Hein M, Lanquart JP, Loas G, Hubain P, Linkowski P. Prevalence and risk factors of type 2 diabetes in insomnia sufferers: a study on 1311 individuals referred for sleep examinations. *Sleep Med.* 2018;46:37-45.
- ²⁷ NICE Clinical Knowledge Summaries [Available from: <https://cks.nice.org.uk/topics/insomnia/>] Accessed on May 2022.
- ²⁸ Stone KL, Ensrud KE, Ancoli-Israel S. Sleep, insomnia and falls in elderly patients. *Sleep Med.* 2008;9 Suppl 1:S18-22.
- ²⁹ Daley M, Morin CM, LeBlanc M, Grégoire JP, Savard J, Baillargeon L. Insomnia and its relationship to health-care utilization, work absenteeism, productivity and accidents. *Sleep Med.* 2009;10(4):427-38.
- ³⁰ Gustavsson A, Svensson M, Jacobi F, Allgulander C, Alonso J, Beghi E, et al. Cost of disorders of the brain in Europe 2010. *Eur Neuropsychopharmacol.* 2011;21(10):718-79.
- ³¹ Heesch CB. The long-term use of sedative hypnotics in chronic insomnia. *Mental Health Clinician.* 2014;4(2):78-81.
- ³² Medicines associated with dependence or withdrawal symptoms: safe prescribing and withdrawal management for adults. NICE guideline [NG215]: NICE; 2022 [Available from: <https://www.nice.org.uk/guidance/ng215>] Accessed on May 2022.
- ³³ Idorsia Pharmaceuticals Ltd. Data on file. Idorsia insomnia market research: May 2022 GP Omnibus results. 2022.
- ³⁴ Data on file. EUCan HCP Databook - Country Breakdowns May 2022.
- ³⁵ Sleepio to treat insomnia and insomnia symptoms. Medical technologies guidance [MTG70]: NICE; 2022 [Available from: <https://www.nice.org.uk/guidance/mtg70>] Accessed on May 2022.
- ³⁶ Overview - Cognitive behavioural therapy (CBT): NHS; [Available from: <https://www.nhs.uk/mental-health/talking-therapies-medicine-treatments/talking-therapies-and-counselling/cognitive-behavioural-therapy-cbt/overview/>] Accessed on May 2022.
- ³⁷ Matthews EE, Arnedt JT, McCarthy MS, Cuddihy LJ, Aloia MS. Adherence to cognitive behavioral therapy for insomnia: a systematic review. *Sleep Med Rev.* 2013;17(6):453-64.
- ³⁸ Rob Newson AD. Cognitive Behavioral Therapy for Insomnia (CBT-I) 2022 [Available from: Cognitive Behavioral Therapy for Insomnia (CBT-I)] Accessed on June 2022.
- ³⁹ Cunningham JEA, Jones SAH, Eskes GA, Rusak B. Acute Sleep Restriction Has Differential Effects on Components of Attention. *Frontiers in Psychiatry.* 2018;9.
- ⁴⁰ Taylor S AF, Burkinshaw P, Greaves F, Kelleher M, Knight, J PC, Tran A, White M, Marsden J. Dependence and withdrawal associated with some prescribed medicines. An evidence review. : Public Health England, London, 2019; 2020 [Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/940255/PHE_PMR_report_Dec2020.pdf] Accessed on May 2022.
- ⁴¹ Brett J, Murnion B. Management of benzodiazepine misuse and dependence. *Aust Prescr.* 2015;38(5):152-5.
- ⁴² Data on file. IQVIA Longitudinal patient data (LPD) 2021.
- ⁴³ Mignot E et al. (2022) Safety and efficacy of daridorexant in patients with insomnia disorder: results from two multicentre, randomised, double-blind, placebo-controlled, phase 3 trials. *Lancet Neurol* 2022; 21: 125–39
- ⁴⁴ Kunz D et al (2022) Long-Term Safety and Tolerability of Daridorexant in Patients with Insomnia Disorder. *CNS Drugs.* 2022 Dec 9. doi: 10.1007/s40263-022-00980-8.
- ⁴⁵ IQVIA MIDAS. Available from: <https://www.iqvia.com/solutions/commercialization/brand-strategy-and-management/market-measurement/midas>.
- ⁴⁶ Office of National Statistics (2020), Estimates of the population for the UK, England and Wales, Scotland and Northern Ireland available from <https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/datasets/populationestimatesforukenglandandwalesscotlandandnorthernireland>

Prescribing Information

Great Britain and Northern Ireland

QUVIVIQ ▼ 25 mg and 50 mg film-coated tablets (daridorexant)

Important note: Before prescribing, consult the full SmPC.

Presentation

Daridorexant 25 mg and 50 mg film-coated tablets

Therapeutic 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.

Posology and method of administration

Recommended dose: one tablet of 50 mg once per night, taken orally in the evening within 30 minutes before going to bed. The maximum daily dose is 50 mg.

For patients with moderate hepatic impairment, or taking moderate CYP3A4 inhibitors, or CNS depressants (based on clinical judgement) the recommended dose is 25 mg once per night.

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

If a dose is forgotten at bedtime, that dose should not be taken during the night. The consumption of grapefruit or grapefruit juice in the evening should be avoided.

Contraindications

- Hypersensitivity to daridorexant or any of the excipients
- Narcolepsy
- Concomitant use with strong CYP3A4 inhibitors

Warnings and precautions for use

Use with caution in elderly patients because of the general risk of falls. Efficacy and safety data in patients >75 are limited.

Patients should be cautioned about drinking alcohol during treatment.

Use with caution when prescribing with CNS-depressant medicinal products due to potentially additive effects and consider a dose adjustment of either QUVIVIQ or the CNS depressant.

Sleep paralysis and hypnagogic/hypnopompic hallucinations can occur, mainly during the first weeks of treatment. Symptoms similar to mild cataplexy have been reported with dual orexin receptor antagonists. Prescribers should explain this to patients and should consider discontinuing treatment depending on the nature and severity of any events.

Use with caution in patients exhibiting symptoms of depression. Suicidal tendencies may be present in patients with depression and protective measures may be required.

Use with caution in patients with psychiatric co-morbidities due to limited efficacy and safety data.

Daridorexant did not have significant respiratory effects in patients with mild or moderate obstructive sleep apnoea (OSA) or moderate chronic obstructive pulmonary disease (COPD). In the absence of data, use with caution in patients with severe OSA and severe COPD.

There was no evidence of abuse or withdrawal symptoms indicative of physical dependence upon treatment discontinuation in clinical studies with daridorexant in subjects with insomnia. 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.

Use is not recommended in patients with severe hepatic impairment.

Interactions

Contraindicated with strong CYP3A4 inhibitors. Use with moderate or strong CYP3A4 inducers may reduce efficacy. Caution should be used in case of simultaneous administration of QUVIVIQ with sensitive substrates of CYP3A4, or of P-gp, with close monitoring in the case of medicinal products with a narrow therapeutic index (e.g. digoxin). The consumption of grapefruit or grapefruit juice in the evening should be avoided. Refer to full SmPC for further information on interactions.

Fertility, pregnancy and lactation

Use during pregnancy only if the clinical condition of the pregnant woman requires treatment with QUVIVIQ. Avoid use during breast-feeding because a risk of excessive somnolence to the breastfed infant cannot be excluded.

Effects on ability to drive and use machines

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

Undesirable effects

Common ($\geq 1/100$ to $< 1/10$): headache, somnolence, dizziness, nausea, fatigue.
Consult the full SmPC for further information on side effects.

Overdose

General symptomatic and supportive medical care should be provided. Adverse reactions at supra-therapeutic doses may include somnolence, muscular weakness, disturbance in attention, fatigue, headache and constipation.

Packaging quantity and storage conditions

Blisters packed in cartons of 10 or 30 film-coated tablets.

Marketing Authorisation Holder and Numbers

Idorsia Pharmaceuticals Deutschland GmbH
Marie-Curie-Strasse 8
79539 Lörrach
Germany

Great Britain: PLGB 48711/0002-0003
Northern Ireland: EU/1/22/1638/001-006

Cost

QUVIVIQ 25 mg x 30 tablets and QUVIVIQ 50 mg x 30 tablets: £42 per pack

Prescription conditions

Prescription only medicine.

Adverse events must be reported. Healthcare professionals are asked to report any suspected adverse reactions via www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in Google play or Apple App store. Adverse events should also be reported to ds.safety.uk@idorsia.com

Date of last revision of prescribing information
September 2023

Job Number: UK-DA-00009

Date of preparation: October 2023 36