National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Daridorexant for treating insomnia disorder

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Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	IDORSIA Pharmaceuticals	Yes, it is appropriate to refer daridorexant for appraisal due to the considerable unmet need in the treatment of insomnia disorder. Insomnia disorder is a chronic condition and current pharmacological treatments are only approved for short term use. Most current pharmacological treatment options also carry considerable safety risks and adverse events (even with short term use), including but not restricted to, next-morning residual effects and the risk of longer term tolerance and dependence. In addition, current pharmacological treatments are limited in their ability to address three critical components of the disease concurrently, i.e. difficulties with sleep onset, poor sleep maintenance, and impairment of daytime functioning.	Thank you for your comment. No action required.
Wording	IDORSIA Pharmaceuticals	The wording of the remit seems appropriate, provided the aspect of chronicity and impairment in daytime functioning are taken into account. The proposal for alternative wording is to specify "for treating insomnia disorder" (rather than "for treating insomnia"), to reflect the population included in the Phase 3 studies, since the concept and definition of insomnia disorder include these two aspects of chronicity and impaired daytime functioning.	Thank you for your comment. The remit was discussed at the scoping workshop, and it was agreed that changing the wording to 'insomnia disorder' was

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		[redacted]	appropriate. The remit has been updated to reflect this.
Timing Issues	IDORSIA Pharmaceuticals	Daridorexant is a novel treatment for Insomnia disorder. The NICE Clinical Knowledge Summary for Insomnia states that Pharmacotherapy should be restricted to short term use only. There is significant current unmet need for patients suffering with insomnia disorder, resulting in impacts on patient QoL, short and long term health and productivity.	Thank you for your comment. No action required.

Comment 2: the draft scope

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Background information	IDORSIA Pharmaceuticals	The background is well-described. However, the focus should be on insomnia disorder pharmacotherapy, and not on the short-term pharmacotherapy that is described in "NICE Clinical Knowledge Summary (CKS) for insomnia" and in the last paragraph of the Background.	Thank you for your comment. The scope aims to provide a general overview of the topic. No action required.
The technology/ intervention	IDORSIA Pharmaceuticals	The description in the Scope for daridorexant is accurate.	Thank you for your comment. No action required.
Population	IDORSIA Pharmaceuticals	The Patient population stated in the draft scope is not correctly defined. Patients included in the phase 3 development program for daridorexant met the DSM-5 criteria for Insomnia Disorder. The DSM-5 criteria is multi-faceted but critically establishes the insomnia as chronic in nature i.e.	Thank you for your comment. The population was discussed at the scoping workshop, and

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		'The sleep difficulty occurs at least 3 nights per week' AND *'The sleep difficulty is present for at least 3 months'* (full DSM-5 criteria outlined in Population section of this document) The target population for the appraisal of daridorexant should be: The treatment of adult patients with insomnia disorder.[redacted] The choice of strategy to treat insomnia depends upon both the duration and nature of the presenting symptoms. DSM-5, the 3rd edition of the International Classification of Sleep Disorders [Sateia 2014], the European guideline for the diagnosis and treatment of insomnia [Riemann, 2017], and the British Association for Psychopharmacology guidelines [Wilson, 2019], all define insomnia disorder as a chronic condition. According to DSM-5, insomnia disorder is defined as: *A) "a predominant complaint of dissatisfaction with sleep quantity or quality with one (or more) of the following symptoms: (i) difficulty initiating sleep, (ii) difficulty maintaining sleep characterized by frequent awakenings or problems returning to sleep after awakenings, and (iii) early-morning awakening with inability to return to sleep* *B) The sleep disturbance causes clinically significant distress or impairment with detrimental effects on daytime functioning, including social, occupational, educational, academic, behavioral, or other important areas of functioning* *C) The sleep difficulty occurs at least 3 nights per week* *D) The sleep difficulty is present for at least 3 months* *E) sleep difficulty occurs despite adequate opportunity to sleep* *F) its not explained by and does not occur exclusively during the course of another sleep - wake disorder* *G) its not attributable to the physiological effects of a substance and*	it was agreed that changing the wording was appropriate. The scope population has been updated to 'adults with insomnia disorder'.

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		H) coexisting mental disorders and medcial conditions do not adequately explain the predominant complain of insomnia " (ref: DSM-5)" Daridorexant is proposed for the treatment of adult patients with insomnia disorder as per population studied during the phase 3 registrations program. The results of the daridorexant Phase 2 (Zammit et al 2020; Dauvilliers et all 2020) and 3 trials have shown that, within insomnia disorder, there is no subgroup that should be considered separately since the efficacy and safety of the product did not differ according to sex, BMI, or across a broad range of ages up to ≥75 years (data on file). There were too few non-White subjects to draw a firm conclusion on race, but no signal of divergent effect was detected. Daridorexant is safe and effective across the full range of insomnia disorder severity as measured by the ISI scale.	
Comparators	IDORSIA Pharmaceuticals	The currently available pharmacological treatments for insomnia disorder are not approved for long term use and should therefore not be considered as comparators for daridorexant. The following statements for the use of pharmacological options for managing long-term insomnia in the UK are taken from the NICE Insomnia Clinical Knowledge Summary (https://cks.nice.org.uk/insomnia#!topicSummary): *"Pharmacological therapy should be avoided in the long-term management of insomnia, however:* - *For some people with severe symptoms or an acute exacerbation a short course of a hypnotic drug (preferably less than 1 week) may be considered as a temporary adjunct to behavioural and cognitive treatment.* o *Do not prescribe long-term hypnotic treatment — for information on withdrawal of hypnotic medication, see the CKS topic on Benzodiazepine and z-drug withdrawal.*	Thank you for your comment. The relevant comparators were discussed at the scoping workshop. It was noted by clinical experts and patient group representatives that access to CBT-I varies geographically. They also noted that CBT-I is not always offered. At the workshop, attendees also discussed pharmacological treatments for insomnia. They explained that

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		- *For people over 55 years of age with persistent insomnia, treatment with a modified-release formulation of melatonin may be considered.*
		  ○ *The recommended initial duration of treatment is 3 weeks. If there is a response to treatment, continue for a further 10 weeks only.*
		  ○ *Discuss the risks (similar to those of other hypnotics including falls, and fractures) associated with melatonin treatment in the elderly.*
		- *Do not recommend over-the-counter treatments for insomnia".*
		
		In the European Guidelines for the diagnosis and treatment of insomnia (Reimann et al. 2017), Cognitive Behavioural Therapy for insomnia, (CBT-I) is recommended as the first-line treatment for chronic insomnia in adults of any age (strong recommendation, high-quality evidence). A pharmacological intervention can be offered if CBT-I is not sufficiently effective or not available. Benzodiazepines, non-benzodiazepine benzodiazepine receptor agonists (also known as z-drugs), and some antidepressants are effective in the short-term treatment of insomnia (≤ 4 weeks; weak recommendation, moderate-quality evidence). Antihistamines, antipsychotics, melatonin, and phyto-therapeutics are not recommended for insomnia treatment (strong to weak recommendations, low- to very-low-quality evidence).
		
		GABA acting drugs (benzodiazepines and Z-drugs) are only indicated for use up to 4 weeks which limits their use in patients with insomnia disorder and therefore such drugs are not relevant comparators for daridorexant which has efficacy and safety data for longer term use.
		
		In adults, the melatonin EU label states it is indicated as monotherapy for the short-term treatment of primary insomnia characterized by poor quality of sleep in patients aged ≥55 years''. Because of the age restrictions, melatonin cannot be used as a comparator for daridorexant.
			none of the currently approved pharmacological treatments are recommended for long term use. Daridorexant is expected to be used to treat insomnia disorder, where symptoms last for more than 3 months per clinical trials. Therefore, the attendees agreed that none of the comparators listed in the draft scope are relevant. The scope has been updated to remove the comparators.

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		Finally, in line with available guidelines, a pharmacological treatment should be started after CBT-I. Therefore CBT-I should not be used as a comparator for daridorexant. In summary, daridorexant may be used in patients with insomnia disorder. Daridorexant showed clinical efficacy for up to 12 months treatment duration (Study 301. 302, including a placebo-controlled extension phase) and the target label aims to reflect such data in the clinical indication of daridorexant. In conclusion, none of the treatments contained within the draft scope are appropriate comparators for daridorexant.	
Outcomes	IDORSIA Pharmaceuticals	Yes, the outcomes proposed in the draft scope are the most important with the following comments: • Resolution of symptoms The global development programme for daridorexant was designed to comprehensively encompass the multiple facets of insomnia defined by DSM-5, covering night-time and daytime symptoms of insomnia (see table below). The improvement of each of the baseline sleep and daytime disturbances was measured during the confirmatory clinical trials. • Changes in sleep patterns and architecture Sleep patterns such as reduction in time to fall asleep, reduction in waking up during the night and increased total sleep time have been demonstrated objectively and subjectively using PSG or sleep diary respectively.	Thank you for your comment. Outcomes were discussed at the scoping workshop, and attendees agreed that the scope included the most relevant outcomes.

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		In addition, objective measurements of sleep architecture were assessed by PSG in the global development programme. • Sleep quality Dissatisfaction with quality of sleep is an important complaint from patients with insomnia, in addition to insufficient quantity of sleep. Quality of sleep was, therefore, also assessed in the daridorexant program using a visual analogue scale completed by the patients every morning during the entire clinical trial duration. • Daytime functioning In keeping with the DSM-5 criteria for insomnia disorder, the EMA guidelines and its importance to patients, Idorsia included an assessment of daytime functioning in the Phase 3 programme. IDSIQ (see attached reference) is a validated questionnaire that allows the assessment of the daytime impact of insomnia on three important dimensions; physical (sleepiness domain), cognitive (alert/cognition domain), and affective (mood domain). The questionnaire has a recall period of “today”, and was completed daily, in the evening, by patients participating in the Phase 3 studies. In addition to the IDSIQ, two VASs were included in the daridorexant clinical programme. The VASs were completed each evening and assessed daytime alertness (“Rate your daytime alertness today” from “very sleepy” to “wide awake and alert”) and daily ability to function (“Rate your daily ability to function today” from “poor” to “excellent”). • Recurrence of insomnia	

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		The confirmatory studies were of 3 months' duration, corresponding to the definition of insomnia disorder. Efficacy over a longer period of treatment, up to 9 months in addition to the chronic treatment described above (for a total of 12 months) was explored in the long-term placebo-controlled extension study 303. Recurrence of insomnia was not measured directly in the clinical studies but the long-term effect of daridorexant, up to 1 year of treatment, was demonstrated. • Adverse effects of treatment (including next-morning residual effects and memory impairment) In subjects with insomnia disorder, morning sleepiness may result from a disturbed sleep, which may be improved by treatment, or from a residual effects of the insomnia medication. The net balance of these opposite effects needed to be thoroughly studied; therefore, next-morning residual effects were systematically assessed in all studies of daridorexant in subjects with insomnia disorder (see table below for the Phase 3 studies). Other adverse events were present at a low incidence in the clinical studies, and often at the same incidence as in the placebo group. For instance, somnolence was reported in 2% of patients treated with either daridorexant 50 mg or placebo. Sleep paralysis was reported in 0.3% subjects receiving daridorexant 50 mg, compared to no reports for placebo. Hallucinations were not reported in subjects receiving daridorexant 50 mg nor in the placebo group. • Health-related quality of life. There was no specific questionnaire for health-related QoL in the clinical studies. However, the combination of the patient-reported assessments of sleep quality (using a Visual Analogue Scale), daytime functioning (the IDSIQ	

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		questionnaire), and insomnia severity (the ISI questionnaire) adds up to a broad evaluation of health-related outcomes. In particular, Idorsia will show, in the cost-effectiveness analysis, that the improvement in ISI induced by treatment with daridorexant can be considered as a reliable marker of health-related outcomes.	
Equality and Diversity	IDORSIA Pharmaceuticals	N/A	No action required.
Innovation	IDORSIA Pharmaceuticals	Yes, daridorexant is an innovative treatment for patients suffering from insomnia disorder. Daridorexant effectively improves nighttime symptoms (efficacy on onset and maintenance of sleep) and daytime symptoms (improvement of daytime functioning). Insomnia disorder is a chronic disease (> 3 months), and none of the currently authorized pharmacological treatments in the EU can be used longterm, leaving patients exposed either to living with insomnia disorder or resorting to an off label use of certain classes of drugs such as benzodiazepines (e.g. use beyond the recommended 4 weeks) resulting in a safety risks. Efficacy and safety data of daridorexant have been generated for up to 12 months of cumulative treatment (Studies ID-078A301, and ID-078A302 and long-term study ID-078A303). Results have shown that daridorexant is devoid of next-morning residual effects such as next-morning sleepiness. Daridorexant is also the first agent to demonstrate improvements in daytime functioning using a validated instrument IDSIQ. Efficacy is maintained over time, and no tolerance, rebound insomnia or withdrawal effects have been observed upon treatment discontinuation.	Thank you for your comment. The innovative nature of the technology will be considered by the committee based on evidence presented to it. No action required.

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Questions for consultation	IDORSIA Pharmaceuticals	**1. Is daridorexant likely to be used alone or as an add-on to existing treatments for insomnia?** No trials tested daridorexant as an adjunctive therapy to GABA drugs or any other prescription or over-the-counter drugs used in the treatment of insomnia and therefore daridorexant is not recommended to be added to any pharmacological treatment used in patients with insomnia disorder. Whilst CBT-I was not an exclusion criterion in the registration trials, no data are available on the efficacy of CBT-I alone versus CBT-I in combination with daridorexant. **2. What is the potential for dependence or misuse of daridorexant?** Multiple animal studies showed that daridorexant and its major metabolites did not activate any abuse-related molecular CNS targets at clinically relevant concentrations (data on file). In an abuse potential assessment study including 72 recreational sedative drug users (Ufer et al. 2021), drug-liking VAS Emax (mean; 95% CI) of daridorexant at 50 mg was significantly lower compared to supratherapeutic doses of suvorexant and zolpidem ($p<0.001$), but similar at 100 mg and 150 mg. At each daridorexant dose, drug-liking VAS scores were greater than placebo. The study concluded that daridorexant showed dose-related drug-liking among recreational sedative drug users with lower effects at the highest phase-3 dose, and similar effects at supratherapeutic doses compared to supratherapeutic doses of suvorexant and zolpidem (Ufer et al. 2021). In clinical studies of chronic exposure up to 12 weeks (Studies ID-078A301, and ID-078A302), and in the long-term safety follow-up Study ID-078A303 providing an additional 9 months of chronic exposure, the frequency and nature of reported AEs did not show any evidence or pattern suggestive of	Thank you for your comment. No action required.

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		drug abuse potential. Furthermore, there was no evidence of any withdrawal syndrome after daridorexant treatment discontinuation. Overall, the totality of available data suggests that daridorexant has very low abuse potential and no risk of physical dependence. Misuse is typically informed by real world evidence. Two DORAs, suvorexant and lemborexant, were approved in the United States in 2014 and 2019, respectively, and could offer insights into the nonmedical use and abuse potential of drugs in the same class as daridorexant. A review of the literature and discussion threads and posts by recreational drug users did not reveal a pattern of recreational use to achieve desired non-therapeutic effects. **3. Where do you consider daridorexant will fit into the clinical pathway for insomnia? Do you consider daridorexant to be an option for acute insomnia, chronic insomnia or both?** Daridorexant is a treatment option for insomnia disorder. It targets nighttime as well as daytime symptoms of this chronic condition. This is consistent with the phase 3 trial population. We anticipate patients will be offered sleep hygiene and CBT-I first, as per guidelines, and then daridorexant. **Is it anticipated that there will be a demonstrable QALY gain for people having daridorexant versus the comparators listed in the scope?** Idorsia expects the cost/effectiveness model to show significant incremental benefits in QALY. However, Idorsia is of the opinion that currently approved treatments can only be used short-term and should not constitute the right comparators for the evaluation of incremental QALY in insomnia disorder, i.e. the target population. **What do you consider the size of the eligible population for daridorexant to be?**	

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		Approximately 6% of adults suffer from insomnia as a disorder (Reiman et al. 2017), which is approximately 3 million UK adult patients. Furthermore in a separate 2020 UK household survey when weighted for the UK population, approximately 900,000 adults self reported a diagnosis of insomnia and were treated by pharmacotherapy. An additional 1.83 million with a self-reported insomnia diagnosis did not receive drug treatment (data on file). We expect a proportion of this group to be successfully managed with either CBT-I or short-term pharmacological therapy. Therefore, the actual eligible population for daridorexant is likely to be a subset of the total population. **Are there any subgroups of people in whom daridorexant is expected to be more clinically effective and cost effective or other groups that should be examined separately?** We do not expect significant differences in risk/benefit ratio or cost-effectiveness across populations of patients with insomnia disorder.	

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope