NICE National Institute for Health and Care Excellence

NICE guidance

Daridorexant for treating long-term insomnia

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 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.

1.2 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.

1.3 This recommendation is not intended to affect treatment with daridorexant that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

CBTi is the standard first treatment for people with long-term insomnia after sleep hygiene advice is offered. But access to CBTi varies across the UK, and for some people it does not work or is unsuitable. For this evaluation, the company asked for daridorexant to be considered as a first treatment when CBTi is not available or is unsuitable, and as a second treatment when CBTi has been tried but not worked. This does not include everyone who it is licensed for.

Clinical trial evidence shows that daridorexant improves symptoms of insomnia compared with placebo for 12 months. The effects if it's taken for longer than this are unknown. A condition of the marketing authorisation is that treatment with daridorexant should be reviewed within 3 months and regularly after that.

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 Information about daridorexant

Marketing authorisation indication

2.1 Daridorexant (QUVIVIQ, Idorsia) is indicated for 'the treatment of adult patients with insomnia characterised by symptoms present for at least 3 months and considerable impact on daytime functioning'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for daridorexant.

Price

2.3 The list price for the 50-mg or the 25-mg dose is £1.40 per day (£42 per pack of 30 tablets; company submission).

3 Committee discussion

The evaluation committee considered evidence submitted by Idorsia, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Details of the condition

3.1 Long-term insomnia, also known as chronic insomnia or insomnia disorder, is defined as dissatisfaction with quantity or quality of sleep for 3 nights or more per week for at least 3 months with an effect on daytime functioning. Long-term insomnia has both night-time symptoms and an effect on daytime functioning. This affects subjective and objective dimensions of health. The patient expert described how insomnia negatively affects mental and physical health and emotional wellbeing. They explained that insomnia is more than struggling to sleep, it also affects daytime functioning and social relationships. The patient expert explained that people with insomnia may have different care depending on where they live. They said that people with the condition would benefit from a longer-term treatment option because current medicines can only be used for a short time. The committee concluded that long-term insomnia can substantially affect people's quality of life, and there is an unmet need for longer-term treatment options.

Treatment pathway

First-line standard treatment is cognitive behavioural therapy for insomnia (CBTi)

3.2 The company explained that insomnia is often treated in primary care. For short-term insomnia, sleep hygiene advice is offered. After this, medicines such as

benzodiazepines, zopiclone, zolpidem and melatonin are used for a short time (less than 4 weeks or less than 13 weeks for melatonin, although some people take them for longer than this). The company highlighted the difference between treatments for short-term insomnia and long-term insomnia. It stated that sleep hygiene advice is also offered for long-term insomnia. Then, CBTi is the recommended first-line treatment. But access to CBTi varies across the country. The clinical experts also noted that there are difficulties accessing CBTi. They explained that there is no data on the use of CBTi in the NHS nationally, but research done in London showed that access to CBTi was very poor. Even when CBTi was available, people with insomnia were often not aware of it. The clinical experts added that CBTi has a 70% to 80% response rate and roughly 50% of people whose condition responds to it experience long-term remission. They also noted that NICE's medical technologies guidance recommends Sleepio, a self-help digital sleep improvement programme based on CBTi for insomnia and insomnia symptoms. But some people may struggle with online CBTi and some people do not have access to it. The committee understood that CBTi is the standard first-line treatment for people with long-term insomnia, but access to it varies.

Company's proposed positioning of daridorexant

3.3 The company proposed that daridorexant would be used in primary care for long-term insomnia 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
- a first-line treatment option when CBTi is not available or is unsuitable.

The committee's discussion focused on the company's positioning of daridorexant as a first-line treatment option when CBTi is not available or is unsuitable. The committee was aware that access to CBTi varies across the country (see section 3.2) and treatment effects may also vary. It understood that this may also be related to the lack of resources for either referral or signposting to CBTi by GPs. One of the clinical experts emphasised that, when possible, GPs should be encouraged to explore reasons why CBTi is

not available during diagnosis and signpost people to have CBTi treatment first. During consultation, a consultee noted that, given the capacity issues in primary care, exploring unavailability of CBTi treatment would be impractical for GPs. The committee agreed with the clinical expert, but acknowledged the NHS capacity challenges and noted that it may be unfeasible for GPs to investigate or address the lack of CBTi services. So integrated care boards should try to ensure that CBTi is available within their area. The committee concluded that the company's positioning of daridorexant as a second-line treatment option for long-term insomnia, when digital or face-to-face CBTi has been tried but not worked, or as maintenance treatment for managing longer-term symptoms, was appropriate. It also concluded that positioning daridorexant as a first-line treatment option when CBTi is not available or is unsuitable was acceptable. But when available and suitable, CBTi should always be offered before daridorexant.

Comparator

3.4 The company provided evidence on daridorexant compared with placebo (see section 3.7). Because CBTi should be the first-line treatment when available and suitable, the committee agreed it was not an appropriate comparator. So it agreed that placebo was the appropriate comparator for decision making.

Diagnosis of long-term insomnia

3.5 The committee noted that daridorexant would be offered mainly in primary care by GPs. It discussed how GPs would diagnose long-term insomnia and how this tied in with the population enrolled in study 301, the pivotal trial for daridorexant (see section 3.7). The clinical experts explained that there are criteria for diagnosing long-term insomnia, but in practice it would also be based on patient experience. GPs would assess perception of sleep quality, sleep quantity and any daytime symptoms. During consultation, the clinical experts flagged that other common sleep disorders (for example sleep apnoea and restless legs) mimic symptoms of insomnia. These sleep disorders can be difficult for GPs to diagnose and prescription of long-term medications for insomnia may risk leaving other

conditions undiagnosed for longer. The clinical experts also explained that the natural history of insomnia varies. Acute insomnia may be resolved in the short term. But once it has lasted for more than 6 months, it may last for years and be difficult to resolve. The committee, which includes GPs, discussed the lack of guidance on insomnia in the UK and highlighted the importance of considering differential diagnoses before prescribing medicine for long-term insomnia. The committee understood that the time constraint of a GP appointment can be a barrier to this. The clinical experts also noted that if recommended, daridorexant would be new to primary care. They explained that it would be good to have a longer-term treatment option in primary care. The clinical experts highlighted that, if daridorexant were recommended, support and training of GPs would be key for its implementation because people's experience of the condition is subjective. During consultation, the company noted there are UK guidelines on insomnia to guide GPs, such as the NICE clinical knowledge summary on insomnia and the British Association for Psychopharmacology consensus statement (Wilson et al. 2019). The company would provide additional support and education to prescribers of insomnia medicine in the NHS, noting that if recommended, daridorexant would be the first medicine available to GPs for the longer-term treatment of long-term insomnia.

Concomitant treatments

3.6 The EAG highlighted that people could have other treatments at the same time as the randomised treatments in the company's pivotal trials, study 301 and study 303. CBTi was allowed if it had been started 4 or more weeks before baseline and continued throughout the studies. Non-prohibited medicines that were part of people's normal care were also allowed. People in both arms took sleep hygiene measures during the study. The committee discussed whether daridorexant, if recommended, could be used alongside other medicines and non-medicine treatments in practice. The clinical experts explained that sleep hygiene measures are still important when having medicine. They reiterated that sleep hygiene measures and behavioural changes for people with insomnia are essential to maximise the treatment effect of daridorexant. They also explained that other treatments for insomnia work in a different way to daridorexant, in that they help with falling asleep. Daridorexant, in comparison, also helps with staying asleep. The committee understood that if daridorexant were recommended,

ongoing support with behavioural changes or sleep hygiene would still be necessary and important. It considered that the comparative effectiveness evidence from the trials was appropriate for decision making. The committee concluded that, if recommended, daridorexant could be used at the same time as other medicines or non-medicine treatments available in practice.

Clinical evidence

Clinical-effectiveness evidence

3.7 The clinical-effectiveness evidence was from study 301 and its extension study, study 303. Study 301 was a phase 3 double-blind randomised controlled trial with 930 people with long-term insomnia. They were randomly assigned to have daridorexant 25 mg (n=310), daridorexant 50 mg (n=310) or placebo (n=310) for 12 weeks. The company only presented evidence for the 50-mg dose of daridorexant compared with placebo in its submission. The double-blind treatment period was followed by a placebo run-out period in which people had once-daily single-blind placebo treatment, and then an unblinded safety follow-up period. Key inclusion criteria for study 301 and study 303 were:

- a diagnosis of insomnia disorder (referred to as long-term insomnia in this guidance) according to the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) criteria, and
- an insomnia severity index (ISI) score of at least 15.

Key exclusion criteria included:

- concomitant CBTi unless started at least 1 month before visit 3 (baseline time point) and continued throughout the study
- mental health conditions diagnosed by the Mini International Neuropsychiatric Interview as 'acute or unstable'
- concomitant CYP3A4 inhibitors.

The primary efficacy endpoints in study 301 were change in:

- wake after sleep onset (WASO) from baseline to month 1 and month 3
- latency to persistent sleep (LPS) from baseline to month 1 and month 3.

Study 303 was primarily a comparative safety study, but it included placebo-controlled subjective outcomes to assess the long-term maintenance effect of daridorexant. People who had daridorexant in study 301 or study 302 (another phase 3 double-blind randomised controlled trial) continued having the same dose in study 303 (n=137). Those assigned to placebo in study 301 or study 302 were re-randomised to have either placebo (n=128) or daridorexant 25 mg in study 303. The treatment period lasted 40 weeks in study 303 (total follow-up time from study 301 and study 303 was 12 months). The primary outcome measure for study 303 was the total number of people with at least 1 treatment-emergent adverse event. The committee noted that evidence from study 302, in which 924 people with long-term insomnia were randomly assigned to have daridorexant 10 mg (n=307), daridorexant 25 mg (n=309) or placebo (n=308) for 12 weeks, was not presented. This is because the company only considered evidence for the 50-mg dose of daridorexant relevant for the submission. At the first committee meeting (from here, referred to as the first meeting), the committee requested that clinical evidence on the 25-mg dose from study 302 should also be provided. The company provided this during consultation. The studies are discussed in sections 3.8 and 3.9.

Additional clinical-effectiveness evidence on the 25-mg dose

3.8 Study 201 was a phase 2, randomised, double-blind, placebo-controlled and active-controlled dose–response study with 360 people with long-term insomnia. They were randomly assigned to have placebo (n=60), daridorexant 5 mg (n=60), 10 mg (n=59), 25 mg (n=60), 50 mg (n=61) or zolpidem 10 mg (n=60) for 30 days. At the first meeting, the EAG was concerned that study 201 was not included in the company's clinical-effectiveness results. The company explained that this study was not designed to evaluate the efficacy and safety of daridorexant compared with placebo because of the small sample size. It added that outcomes were assessed on days 1 and 2 only and were not deemed relevant to the treatment of long-term insomnia. A clinical expert noted that daridorexant is a

new medicine with limited evidence. So, they would consider this study relevant despite the limitations, because it would increase the evidence base. The clinical experts said that in clinical practice, GPs may start from the lower 25-mg dose and titrate up to the 50-mg dose if needed. The committee acknowledged that unlike longer 12-week follow-up studies like study 301 and 302, study 201 was a dose–response study with only 28 days of follow up. But it concluded that alongside the evidence on the 25-mg dose from study 302 (see section 3.7) it would like to see evidence on the treatment effect of the daridorexant 25-mg and 50-mg doses from study 201. During consultation, the company provided daridorexant 25-mg clinical-effectiveness evidence from study 201 and study 302, along with 25-mg data from study 301 and 303.

Clinical-effectiveness results

Effect of daridorexant 50 mg on WASO and LPS

3.9 In study 301, there were greater reductions from baseline in WASO and LPS for daridorexant 50-mg compared with placebo at month 1 and month 3. For WASO, the least squares mean (LSM) difference was 22.78 minutes [p<0.0001] and 18.30 minutes [p<0.0001], at months 1 and 3 respectively. Similarly, for LPS, the LSM difference was 11.35 minutes [p<0.0001] and 11.67 minutes [p<0.0001], at months 1 and 3 respectively. The company explained that these objective measures were used as the primary outcomes for regulatory approval. The clinical experts explained that daridorexant is a medicine for sleep maintenance. They noted that the differences in WASO and LPS can be considered clinically meaningful but emphasised that in practice, subjective improvements in sleep quality, sleep quantity and daytime symptoms are more important than measures such as WASO and LPS.

Effect of daridorexant 25 mg on WASO and LPS

3.10 Both study 201 and study 302 showed greater reductions and improvement from baseline in the primary endpoint WASO for daridorexant 25 mg compared with placebo. The LSM difference on days 1 and 2 in study 201 was -16.2 minutes (p=0.007) and in study 302 at months 1 and 3 was -11.62 minutes (p=0.0001) and

10.25 minutes (p=0.0028) respectively. Both studies also showed improvement from baseline for daridorexant 25 mg compared with placebo in LPS. These improvements were not statistically significant at month 1 or 3 in study 302. The company noted that even though daridorexant 25 mg improved some sleep variables, the magnitude of improvement was lower than with the 50-mg dose.

Effect of daridorexant 50 mg on ISI score

3.11 The ISI score was an exploratory outcome in study 301 and study 303 and was the only efficacy outcome the company used to inform its economic modelling. The ISI has 7 questions and the total score, ranging from 0 to 28, is the sum of the scores for each of the questions. Higher scores indicate more severe insomnia. Reductions from baseline in ISI score were greater for daridorexant 50 mg than placebo at both month 1 and month 3 in study 301. At month 1, the reduction from baseline in mean ISI score was 4.9 (standard deviation [SD] 5.5) for daridorexant and 3.1 (SD 4.7) for placebo. At month 3, the reduction from baseline in mean ISI score was 7.2 (SD 6.5) for daridorexant and 5.4 (SD 5.7) for placebo. The EAG did a between-arm analysis for ISI score at 3 months, which showed a mean difference of -1.8 (95% confidence interval 2.74 to -0.85). The clinical experts commented that a difference of at least 4 in a between-arm analysis for ISI score would be considered clinically meaningful but noted that the placebo effect in this case was substantial. They also noted that in clinical practice, only people who benefit from treatment would continue, so it can be expected that a larger reduction would be seen in clinical practice. The ISI score results for the 50-mg dose from study 303 are considered confidential and cannot be reported here. At the first meeting, while there was uncertainty about whether the difference was clinically meaningful, the committee concluded that the daridorexant 50-mg dose may be associated with a greater reduction in ISI scores than placebo.

Effect of daridorexant 25 mg on ISI score

3.12 For the daridorexant 25-mg dose studies, the ISI score was an 'other efficacy endpoint' in study 201 and an exploratory efficacy endpoint in studies 301 and 302. The absolute change in ISI score from baseline to day 30 was similar

between placebo and daridorexant in study 201 (placebo: mean -7.7 [SD 5.4]; daridorexant 25 mg: -7.9 [SD 5.9]). In study 301, the absolute change from baseline to month 3 was similar between placebo and daridorexant (placebo: -5.4 [SD 5.7]; daridorexant 25 mg -6.0 [SD 5.8]). In study 302, daridorexant 25 mg demonstrated greater reduction in mean ISI scores from baseline at both month 1 and month 3 compared with placebo (month 1: -5.1 [SD 5.2] versus -3.8 [SD 4.6]; month 3: -6.9 [SD 6.0] versus -5.4 [SD 5.5]). The company considers the ISI results for the 25-mg dose from study 303 to be confidential, so they cannot be reported here.

The company's modelled ISI outcomes

3.13 In the company's consultation response, they provided the mean ISI outcomes from study 301 and 303 and the modelled ISI outcomes from study 301, 302 and 303. The company noted that when comparing the effects on ISI score from studies 301 and 303 for the different doses, daridorexant 50 mg was more clinically effective than daridorexant 25 mg across all modelled time points. These results are also consistent with the outcomes of study 201. The committee acknowledged the ISI score results for the 25-mg dose across the different studies. It concluded that the 50-mg dose appeared to be superior compared with the 25-mg dose.

Effect of daridorexant 50 mg on other exploratory outcomes

3.14 Some other exploratory outcomes were assessed in study 301 and study 303, including:

- total sleep time
- the Insomnia Daytime Symptoms and Impacts Questionnaire score
- the Patient Global Assessment of Disease Severity score
- the Patient Global Impression of Change score and
- sleep efficiency (%).

The company and EAG did between-arm analyses for the outcomes; that is, the mean difference in change from baseline in the outcome on daridorexant 50 mg minus the mean difference in change from baseline on placebo. For most outcomes, daridorexant 50 mg showed a statistically significant reduction in insomnia compared with placebo at 3 months. But the EAG noted that the benefits of daridorexant 50 mg compared with placebo at 3 months did not appear to persist at 12 months for some outcomes (the exact outcomes are considered confidential and cannot be reported here). The committee noted that there was no clinical data beyond 12 months. The clinical experts stated that it was difficult to predict long-term treatment effect without data beyond 12 months, but noted that people would stop treatment if they were no longer benefitting. The committee concluded that daridorexant 50 mg was largely effective in improving symptoms related to long-term insomnia at 12 months, and acknowledged uncertainties about the duration and extent of benefit of treatment beyond 12 months.

Effect of daridorexant 25 mg on other exploratory outcomes

3.15 Study 302 showed benefits with daridorexant 25 mg based on subjective assessments of sleep severity and quality. Changes from baseline in visual analogue scale (VAS) scores from the Sleep Disorders Questionnaire (SDQ; quality and depth of sleep, daytime alertness, ability to function) were greater for daridorexant 25 mg than for placebo. For study 201, the 25-mg daridorexant dose showed higher mean self-reported VAS scores for sleep quality, morning sleepiness, and daytime alertness compared with placebo. During consultation, the company provided a meta-analysis in which the data on night (WASO, LPS and subjective total sleep time) and daytime (Insomnia Daytime Symptoms and Impacts Questionnaire) outcomes were pooled for the 50-mg and 25-mg doses from studies 201, 301 and 303. The company summarised that the analysis showed that the 25-mg dose is less clinically effective than the 50-mg dose. The committee acknowledged the other exploratory outcomes for the 25-mg dose across the different studies.

Safety results

3.16 In study 301, during the double-blind study period, treatment-emergent adverse events were reported in 37.7% (117 out of 310), 37.7% (116 out of 308) and 34.0% (105 out of 309) of people in the daridorexant 25-mg, 50-mg and placebo arms, respectively. Treatment-emergent serious adverse events were reported in 0.6% (2 out of 310), 1.0% (3 out of 308) and 2.3% (7 out of 309) of people in the daridorexant 25-mg, 50-mg and placebo arm, respectively. In study 303, subjects assigned to the placebo group in study 301 and 302 were re-randomised to receive either placebo or daridorexant 25 mg. Study 303 therefore has an ex-placebo arm (from study 301 or 302) who went on to have the 25-mg dose (referred to as 'ex-placebo to 25 mg'). During the double-blind study period, there were treatment-emergent adverse events in 37.7% (101 out of 268), 38.0% (52 out of 137), 33.6% (43 out of 128) and 38.1% (48 out of 126) of people in the daridorexant 25-mg and 5-mg arms, placebo arm and the ex-placebo to 25-mg arm respectively. Treatment-emergent serious adverse events were reported in 4.5% (12 out of 268), 5.1% (7 out of 137), 1.6% (2 out of 128) and 3.2% (4 out of 126) of people in the daridorexant 25-mg and 50-mg arms, placebo arm and the ex-placebo to 25-mg arm, respectively. During consultation, the clinical expert noted that although daridorexant has a better safety profile than some other treatments, some are considered equally safe. For the other 25-mg dose studies provided by the company during consultation (studies 201 and 302), the treatment-emergent adverse events and treatment-emergent serious adverse events were similar across the study arms. The company noted that there was no additional safety advantage or concerns associated with the lower 25-mg daridorexant dose compared with the 50-mg dose. The committee acknowledged the similar safety outcomes for the 25-mg and 50-mg dose across the different studies.

Uncertainty in longer-term treatment effect

3.17 The committee was aware that evidence from study 301 and study 303 indicated that daridorexant's treatment effect compared with placebo at 3 months did not appear to persist at 12 months for some outcomes (see section 3.14). Few participants remained on the daridorexant treatment arm at 12 months and there was no trial evidence on daridorexant's treatment effect beyond 12 months. So,

the committee questioned whether it could be possible for the treatment effect to taper but still provide some marginal benefit. During consultation, the company highlighted that there were few studies evaluating treatment of long-term insomnia, and daridorexant studies provided some of the longest follow-up data. The clinical experts explained that the longer-term treatment effect is unknown because of the lack of evidence. People would stop treatment if there was no benefit but may continue if there is some. The clinical experts also explained that some people may neglect sleep hygiene measures while taking medicine, which could affect the treatment effect. There is a lack of opportunity to find out which behaviours offset the effect of medicines. A clinical expert continued that a 'drug holiday' may also be possible in practice, and some people may continue benefitting from treatment after stopping. The committee agreed that it is important for GPs to reinforce sleep hygiene advice alongside use of medicines in practice. It concluded that the long-term treatment effect of daridorexant is uncertain and took this into account in its decision making.

Generalisability of evidence to NHS population

Selective enrolment criteria of trials

3.18 The committee understood that the DSM-5 criteria of insomnia disorder was one of the criteria used to enrol people in study 301 and study 303. According to the DSM-5 criteria, insomnia disorder is defined as dissatisfaction with sleep quantity or quality, associated with:

- difficulty falling asleep or maintaining sleep
- waking up early without being able to return to sleep
- significant social or functional distress or impairment because of sleep disturbance
- difficulty with sleep at least 3 nights a week and for at least 3 months, despite adequate opportunities for sleep.

The EAG noted that the trial inclusion criteria for study 301 contained specific details on top of the DSM-5 criteria (for example, an ISI score of at least 15,

at least 30 minutes to fall asleep, and wake time during sleep of at least 30 minutes). The EAG further added that this could make the trial population narrower than the population in the NHS. The committee recalled that clinical experts stated that diagnosis of long-term insomnia in practice would also be based on people's experience, which could be subjective. GPs would assess perception of sleep quality, sleep quantity and any daytime symptoms (see section 3.5). The clinical experts added that ISI is not a screening tool so should not be used in clinical practice to diagnose insomnia. During consultation, the company noted that the DSM-5 and ISI criteria were included to assess the nature, severity and impact of insomnia. They were confirmatory criteria and were not used for narrowing the population. The committee concluded that the inclusion criteria for the trial resulted in a narrower trial population than the anticipated treatment population, and accounted for this uncertainty in its decision making.

Excluding mental health conditions

3.19 Study 301 excluded people with 'acute and unstable' mental health conditions. The company explained that 'acute and unstable' was defined in the trial as any mental health condition needing psychoactive medicine. The committee considered this to be very broad and included many chronic conditions. The EAG noted that insomnia frequently occurs alongside mental health conditions. So, excluding people with mental health conditions also results in uncertainty about the generalisability of treatment effect to the anticipated treatment population. The company acknowledged that people with comorbid mental health conditions who need medicine were not included in the trials. This was because it may be challenging to separate the benefits of daridorexant from treatments for mental health conditions. The company added that medicines for mental health conditions are known to affect sleep, have been associated with insomnia, and also modulate neurotransmitters involved in the regulation of the sleep–wake cycle. The clinical experts explained that medicines for insomnia can be offered to people with mental health conditions. So, they would expect that daridorexant would also be offered to people with mental health conditions. The committee noted the importance of differential diagnoses including chronic, stable and comorbid psychiatric diagnoses. It also noted that people with mental health conditions would likely follow the treatment pathway for their condition first

before daridorexant would be considered as a treatment option for long-term insomnia. The committee concluded that excluding people with mental health conditions from the trials may create uncertainty about the generalisability of the clinical evidence, but it understood the company's reasoning for doing this. It noted that daridorexant may be offered to people with mental health conditions in practice and took this into account in its decision making.

Ethnicity

3.20 Study 301 (n=930) reported ethnic groups as follows: 1% Asian, 9.5% Black and 89.5% White. Study 303 reported ethnic groups as follows: 1% Asian, 8.5% Black and 89.5% White. The EAG highlighted that there was a possible difference in the proportions of ethnic groups in the UK population of people with long-term insomnia, and the clinical trial populations. The proportions of ethnic groups in the UK population with long-term insomnia do not appear to be available in the literature. So there is uncertainty about whether proportions of ethnicities in the trial are representative of the UK target population. The EAG commented that if ethnicity is a treatment-effect modifier for daridorexant, differences in ethnicity proportions between study 301 and study 303, and the UK target population, could potentially affect applicability. Study 301 did not subgroup for ethnicity. Also, while study 303 did not find evidence that ethnicity was an effect modifier, analyses were only presented for 2 outcomes. The company explained that published literature suggested that differences in metabolism between ethnic groups are not clinically significant, so it expects that the treatment effect is not affected by ethnicity. The clinical experts stated that in their experience, response to insomnia medicine is not affected by ethnicity. Study 301 and study 303 did not include people from the UK and a clinical expert stated that behaviours affecting sleep quality could differ between the UK and other European countries. The committee understood that currently there is a lack of evidence on whether ethnicity would modify the treatment effect of daridorexant but noted this may add uncertainty to the generalisability of the evidence.

Economic model

Company's modelling approach

3.21 The company presented a novel economic model and stated that it was not aware of any formal terminology to describe the model form. It used multiple regression models to estimate costs and effects for months 1, 3, 6, 9 and 12 based on observed ISI scores from study 301 and study 303. The company explained that it chose ISI to inform the model because there is a lack of data sources to inform the mapping to EQ-5D for other trial outcomes. The time horizon in the company's base-case model was 12 months. The company also presented a lifetime time horizon scenario analysis that explored the epidemiological relationship between poor sleep and poor long-term health outcomes. This included a mortality benefit for daridorexant and improved cost effectiveness compared with the base case. The company explained that a 12-month time horizon was chosen for the base case because this time frame corresponds to the combined period of study 301 and study 303. Extrapolation beyond the available data would be based on assumptions, which would add uncertainty. It further stated that the benefits of daridorexant would apply within hours of starting treatment and would be lost within hours of stopping treatment. So a 12-month time horizon is sufficient and appropriate to estimate cost effectiveness while including dropout rates. The committee understood that long-term insomnia is a chronic condition but the model assessed symptoms related to it as measured by ISI. The committee also understood that there was no evidence on daridorexant's long-term treatment effect (see section 3.14). So, the committee accepted a 12-month time horizon for the base-case analysis.

Dosage

3.22 The committee noted that the marketing authorisation for daridorexant includes the 25-mg and 50-mg doses. At the first meeting the company submission focused on the clinical effectiveness of the 50-mg dose (see section 3.7), and the model included only the 50-mg dose. The company explained that the 25-mg dose is indicated for a subgroup of people with liver problems or who are taking CYP3A4 inhibitor drugs. It added that for this subgroup, the 25-mg dose aims to

achieve '50-mg equivalent' daridorexant plasma levels and that the cost effectiveness is expected to be the same for both doses. The EAG considered that omitting the 25-mg dose presented a problem for population applicability because the results from the trial are not applicable to people with conditions for which the 25-mg dose is indicated (see section 2.2). A clinical expert added that in clinical practice, GPs are likely to start from the lower 25-mg dose and titrate up to the 50-mg dose if needed. The committee acknowledged that the trial data for the 25-mg dose is not applicable to the population for which the summary of product characteristics recommends the 25-mg dose. But, based on clinical expert opinion, the committee considered that people without liver problems or not taking CYP3A4 inhibitor drugs may still start on the 25-mg dose. At the first meeting, the committee concluded that it would like to see a scenario analysis for the cost effectiveness of the 25-mg dose.

Cost effectiveness of daridorexant 25 mg

3.23 In its response to consultation and the committee's request, the company provided a scenario analysis for the cost effectiveness of the daridorexant 25-mg dose. The company provided clinical evidence from study 201, 301, 302 and 303 for the 25-mg dose (see sections 3.7 to 3.17). For the 25-mg dose base-case analysis, the company used ISI clinical efficacy trial data for the first 3 months from study 301, and study 303 was used to inform clinical efficacy beyond 3 months for the daridorexant arm. The company used study 301 in its base case because this study investigated both 25-mg and 50-mg doses and it was considered a more appropriate comparison between the doses. Study 201 was not statistically powered to provide conclusions on efficacy and therefore was not used in the cost-effectiveness analysis. In a scenario, the company used ISI clinical efficacy data for the first 3 months from study 302 instead of study 301. In both analyses the company used the same economic model structure and assumptions as for the daridorexant 50-mg model and a time horizon of 12 months. The company reiterated that the 25-mg dose was less clinically effective compared with the 50-mg dose. They stressed that the 25-mg dose should be used according to the marketing authorisation, as a reduced dose in specific populations. The EAG stated that there was limited evidence to show the 25-mg dose resulted in poorer efficacy outcomes compared with the 50-mg dose, so there was limited evidence to stop the use of the 25-mg dose in the

overall population. The committee acknowledged the scenario analysis provided by the company and recalled that in practice there may be a tendency to start prescribing with a lower dose (see section 3.8). But the committee agreed with the company and concluded that making recommendations outside of the marketing authorisation for daridorexant was not within NICE's remit.

Model comparators

3.24 The decision problem comparator is established clinical management (ECM). The comparator used by the company in the economic modelling was 'no treatment', with the placebo arm of the trial serving as a proxy for no treatment based on the analysis of study 301 (see section 3.7). The company stated that none of the currently approved medicines are recommended for long-term use. It explained that daridorexant is indicated for long-term insomnia with symptoms for at least 3 months, as per the clinical trial. The company reiterated that the proposed positioning for daridorexant is at second-line after CBTi has been tried and not worked, or as a maintenance treatment option for longer-term management of symptoms, or at first-line when CBTi is not available or is unsuitable. So medicines or CBTi cannot be considered ECM or appropriate comparators. The committee recalled that it considered the company's positioning of daridorexant appropriate (see section 3.3). Based on the company's proposed positioning of daridorexant in the treatment pathway after CBTi, unless CBTi is not available or is unsuitable, the committee concluded that 'no treatment' is the appropriate comparator in the model.

Placebo effect

Selective attrition and placebo adjustment

3.25 The ISI scores for both the daridorexant and the placebo arm decreased at each time point in study 301 and study 303. The company's base-case analysis accounted for the placebo effect by assuming that the no-treatment group would continue at the same ISI achieved by the end of study 301 (that is, month 3). The company considered this assumption conservative (compared with ISI scores for the no-treatment group dropping to baseline). It also considered that the

increasing improvement in ISI scores over time in study 303 could be attributed to selective attrition (the selective dropout of some people who systematically differ from those who remain in the study) in both treatment groups. The company added that the trial data showed that people who dropped out of study 303 before the week 40 visit had smaller changes in ISI scores compared with those who completed the study, which supported the selective attrition argument. The EAG explained that the company's approach of accounting for placebo effect by applying the month 3 ISI score was not necessarily conservative and there was uncertainty. The EAG commented that it was unclear whether the improvement in ISI scores over time could be attributed to natural improvement of symptoms, regression to the mean, or the placebo effect. It added that despite a loss of effect between the end of study 301 and beginning of study 303, study 303 continued for 40 weeks more and scores could have improved naturally, especially given that insomnia is highly related to lifestyle factors. In its base case, the EAG preferred to include placebo adjustment for the time horizon of 12 months based on ISI scores in both study 301 and study 303. At the first meeting the committee considered that selective attrition might be a possible explanation for the improvement in ISI scores. But it was not presented with evidence supporting this argument. Given the uncertainties, the committee concluded that it preferred the EAG's base-case assumption, which used the ISI scores from both study 301 and study 303 to inform the ISI for the no-treatment group. But the committee acknowledged that selective attrition might be possible and asked the company to provide additional data or evidence to support this argument.

Additional evidence on selective attrition

3.26 In response to committee's request, the company provided additional evidence for selective attrition and the need to apply a placebo adjustment. This included data on those who completed the 12-month follow up (completers) and those who dropped out before (non-completers). The company provided ISI scores from study 301 (weeks 0 to 12) and study 303 (weeks 13 to 52) for the completers and non-completers per treatment arm. The ISI scores were similar between the non-completers in both treatment arms. The non-completers had smaller ISI improvements compared with the completers. More people dropped out of the placebo arm compared with the daridorexant arm overall in the study

(across all outcomes) because of lack of efficacy. Study 303 captures the outcomes of the better performers in the placebo arm, which would not happen in practice as people would be unable to drop out of 'no treatment'. Therefore the company argued that this placebo adjustment is needed to prevent a selective attrition bias. The company clarified that placebo adjustment was not stopped completely after the first 3 months and that the last observed outcomes of study 301 were still being used for the no-treatment group in the model. For the daridorexant arm, data from study 301 and study 303 was used to model the ISI outcomes for months 1 to 3 and months 3 to 12 respectively.

A range of methods can be used to limit attrition bias

3.27 The EAG noted attrition bias is defined as a 'systematic error caused by unequal loss of participants from a randomised controlled trial' (see Cochrane's tutorial on attrition bias in randomised controlled trials). To limit the bias, statistical solutions such as intention to treat (ITT) analyses are adopted. Last observation carried forward (LOCF) analysis, multiple imputations and worst case scenario analysis are the approaches commonly used to estimate the outcomes for people who did not complete treatment or were lost to follow up. The company used LOCF analysis from study 301 for the no-treatment group and study 303 for the daridorexant arm. The completer and non-completer data for ISI outcomes does not indicate an unequal loss of participants and therefore there is limited evidence supporting the selective attrition bias assumption. The company accounted for the selective attrition in the no-treatment group but not in the daridorexant arm of the model. The EAG explained that adjustments cannot only be applied in 1 arm because selective attrition is observed in both arms. So, amending 1 arm is introducing further bias. Placebo adjustments need to be applied to both arms to cancel out any bias. People discontinuing a placebo arm because of lack of efficacy (or any cause) is a common occurrence in randomised controlled trials (RCTs) and adjusting 1 arm undermines the method of RCTs. The ITT analysis is an established method used to limit such types of differential bias.

The EAG's approach to modelling is appropriate

3.28 The company explained that they agree with Cochrane's selective attrition

definition and that selective attrition does occur in both arms of study 301 and 303. They explained that the large number of dropouts in the placebo arm results in the 'missing data not at random' problem, in which the missing data is systematically related to the unobserved data and therefore related to the events in the trial. This bias cannot be accounted for within an ITT analysis and the company reiterated that in the real world and in the model people would not drop out of 'no treatment'. Furthermore, daridorexant is an 'acute effect' drug with which treatment effect is experienced soon after treatment initiation, and likewise a decline in effect is experienced soon after stopping treatment. This phenomenon is evident from the drop in ISI improvement between study 301 (week 12) and study 303 (week 13). This is different to other treatments assessed in placebo-controlled RCTs that show gradual reductions in treatment effect once treatment is stopped. Because of the unique nature of the acute treatment effect changes being modelled in the daridorexant arm and the large number of dropouts in the placebo arm, an adjustment to the no-treatment group is needed in the model. This is despite the ITT analysis potentially correcting for such types of selective attrition bias. The committee noted that deviating from an ITT approach would:

- result in loss of randomisation benefit
- cause differential treatment of the 2 treatment arms, and
- support the assumption that selective loss of poor responders only occurs in the placebo arm.

The committee was reluctant to move away from the principles of an ITT analysis to assess clinical effectiveness because they mirror actual practice, and are commonly used for most randomised placebo-controlled trials. The committee questioned whether a responder–non-responder model structure might have more appropriately adjusted for the selective attrition bias issue. The company responded that with more time and patient-level data a responder–non-responder analysis may have been more appropriate. The committee acknowledged that daridorexant had an acute effect and understood the company's selective attrition argument but noted uncertainty remained with the way placebo adjustment was applied in the model. Overall, the committee concluded that the ISI scores from both study 301 and 303 should be used to model the ISI outcomes for the no-treatment group, so it

considered the EAG's approach to be more appropriate.

Stopping treatment and treatment effect waning

3.29 The committee noted that the summary of product characteristics for daridorexant does not include a stopping rule. However, it states that treatment duration should be as short as possible, with check-ups within 3 months and periodically after. The committee noted that study 303 reported that less than 10% (the exact data is considered confidential so not reported here) of people on daridorexant 50 mg stopped because of lack of treatment effect. It also noted that in the company's analysis based on patient-level data from the trials, a relatively large proportion of people (the data is considered confidential so not reported here) dropped out from the daridorexant arm at 12 months. The committee recalled the discussion about daridorexant's longer treatment effect (see section 3.17) and the uncertainties related to it. The committee was also aware that daridorexant will mainly be used in primary care as there are not many secondary care sleep services in the UK. Given this, and the lack of data on daridorexant's long-term treatment effect, the committee noted that exploring stopping rules for daridorexant would be important. At the first meeting, the committee concluded that it would prefer to see analyses exploring treatment effect waning and a stopping rule in the company's lifetime time horizon scenario.

The committee prefers a 12-month time horizon

3.30 In response to consultation, the company provided 3 scenarios using the lifetime horizon model to address the committee's request. The first scenario applied a 5% treatment effect waning to the health-related quality of life and mortality benefit outcomes of the daridorexant 50-mg arm in the model. The second scenario applied a 10% treatment effect waning assumption to these same outcomes. Only the quality-adjusted life year (QALY) outcomes were impacted. Cost outcomes remained unimpacted. The third scenario included a 10% treatment effect waning and an 'annual challenge' assumption to address the committee's request for implementing a stopping rule. The annual challenge modelled a yearly GP review cost in which treatment was withdrawn from people

on a yearly basis to assess whether the treatment effect is lost. The company assumed that 20% of people discontinued treatment after the review every year because of a loss of treatment benefit. The committee acknowledged the 3 scenarios provided by the company. It noted that a mortality benefit was modelled in the lifetime horizon model but was unable to explore the basis for this benefit and did not agree with its inclusion. It understood from the company that this had a minimal impact on the incremental cost-effectiveness ratios (ICERs) and therefore agreed that the lifetime horizon model could be suitable for decision making. The committee concluded there were significant uncertainties with the lifetime horizon model. This was because long-term data beyond 12 months for daridorexant was limited, most people had discontinued treatment after the 40-week extension study 303 and healthcare professionals are unlikely to prescribe long-term treatment for insomnia (see section 3.5). The committee preferred the 12-month time horizon model for its decision making.

Adverse events

3.31 The company's economic model did not include adverse events. This was based on the company's opinion that adverse events were not expected to significantly affect health-related quality of life and costs. The EAG stated that it did not expect a large impact on cost-effectiveness results but would prefer all adverse events from study 301 and study 303 to be included in the cost-effectiveness analysis. The committee concluded that the effect of including adverse events in the model is likely to be minor. But at the first meeting, the committee noted that it would prefer the estimated impact of adverse events on costs and QALYs to be included in the economic model. In response to the committee's request, the company included cost and disutility outcomes for all treatment-emergent adverse events occurring in more than 2% in any treatment arm in the economic model base case. The committee acknowledged the inclusion of the adverse event outcomes in the economic model and concluded that the base case should include the impact of adverse events.

Utility values

3.32 The company developed a novel mapping algorithm based on the National Health

and Wellness Survey (NHWS) dataset to map ISI data from study 301 and study 303 to EQ-5D values. The company stated that ISI was used because there were no available data sources to estimate a mapping function for other trial outcomes. The company's base-case model used an adjusted limited dependent variable mixture model to create the mapping function. This model narrowly outperformed a generalised linear model with a gamma distribution family and log link function based on model fitting performance and predictive validity. The EAG was concerned with the lack of a conceptual overlap between ISI and EQ-5D instruments, and the subsequent suitability of the mapping algorithm to estimate health-related quality of life in insomnia. The EAG also had concerns that the population used for developing the mapping algorithm (from the NHWS) was broader than the trial population. The company responded that ISI correlates with EQ-5D and was suitable to estimate QALYs. It added that it is very plausible that the EQ-5D does not fully capture the effect of long-term insomnia on health-related quality of life, so QALY benefits may be underestimated. Regarding the comparability of populations for developing the mapping algorithm, the company stated that the broader range of severity from the NHWS survey than in the clinical trial could be argued as a positive attribute. This is because a broader range of ISI and EQ-5D values should result in a more robust mapping algorithm. The committee concluded that the utility values presented by the company were appropriate for decision making but noted the uncertainties in mapping. It took this into account in its decision making.

Costs

3.33 The company's economic model included treatment costs and medical costs. To estimate the resource use for medical costs, the association between direct healthcare resource use (GP visits, emergency room attendances and inpatient care) and ISI scores was calculated from the NHWS data. This was done using a generalised linear model with a negative binomial distribution family and a log link. The EAG stated that it would prefer all relevant costs to the NHS and personal social services to be included in the economic model. For example, the company did not include concurrent medication costs and outpatient care costs. The committee agreed that including only costs related to GP visits, emergency room attendances and inpatient care was a conservative assumption. The committee recalled the discussion that, if daridorexant were recommended,

further support and training for GPs would be needed for diagnosing long-term insomnia in primary care (see section 3.5). The committee also recalled that reinforcement about currently available treatment options would be important to ensure daridorexant's effective use in primary care. At the first meeting, the committee concluded that it would prefer all costs incurred by the NHS, including providing support and training for GP practices, to be included in the economic model.

Additional costs explored in the company's model

3.34 In response to the committee's request, the company:

- Included additional NHS prescription and outpatient visit costs in its updated base case. The company applied an inflation factor of 1.39 to the direct health costs in the economic model. The inflation factor was based on Wickwire et al. (2019), a US-based study that estimated that inpatient stays and emergency department attendances formed 72% of the direct healthcare costs for people with insomnia. The committee acknowledged the inclusion of the additional NHS costs and concluded that these should be included in the base case.
- Included the impact of GP training costs within a scenario analysis. This assumed costs for 2 hours of GP training per year, which worked out as £10.90 per person with insomnia. The company said that GP training costs have not been included in its base-case analysis because prescription of daridorexant would not need substantial additional support and training for GPs. The EAG explained additional training costs should be included. This is because, according to the company's survey, GPs have lower confidence when prescribing insomnia medication. The committee agreed and concluded that GP training costs should be included in the base case.

Productivity costs should not be included

3.35 In response to consultation, the company noted that the committee did not consider the additional societal value of daridorexant. The company provided a scenario in which the 'Sheehan disability scale' from the clinical trial was used.

This scenario showed daridorexant to be cost neutral. The second scenario used the Work Productivity and Activity Impairment questionnaire from the NHWS, which showed daridorexant to be cost saving. The committee acknowledged these additional scenarios and that there may be uncaptured benefit, but noted that the final scope included reference case cost considerations only from an NHS and personal social services perspective. It concluded that based on sections 5.1.7 to 5.1.10 of the old manual and sections 4.2.7 to 4.2.10 in the new NICE health technology evaluations manual, productivity costs should not be included within the reference case because it was not detailed within the remit from the Department of Health and Social Care and the final scope.

Cost-effectiveness estimates

Uncertainties in evidence and model assumptions

3.36 After the second meeting, the committee noted that some uncertainties were resolved by the new evidence and scenarios presented by the company, including:

- study results from Dauvilliers et al. (2020; study 201) and evidence on the clinical effectiveness of daridorexant 25 mg from studies 301, 302 and 303 (see section 3.7)
- the 25-mg dose of daridorexant assessed in the economic model (see section 3.22)
- adverse events included in the economic analyses (see section 3.31)
- relevant costs to the NHS and personal social services being included in the model, for example, costs to provide support and training for GP practices (see section 3.33).

But the committee noted that some uncertainty remained in the company's clinical evidence and model assumptions. Specifically, these are the:

- uncertainty in whether the difference from baseline in ISI scores between the 2 arms was clinically meaningful (see section 3.11)

- lack of evidence about daridorexant's longer-term treatment effect, including uncertainties in treatment duration as well as extent of benefit of treatment beyond 12 months (see section 3.17 and section 3.29)
- trial populations being narrower than the anticipated treatment population (see section 3.18)
- generalisability of evidence from study 301 and study 303 to UK practice in terms of excluding people with mental health conditions and non-UK based trial locations (see sections 3.18 and 3.19)
- uncertainty about whether ethnicity is a treatment-effect modifier for daridorexant, and the proportion of ethnic groups in trials not representing the UK population with insomnia (see section 3.20)
- uncertainty about whether the improvement in ISI in the placebo arm of study 303 was a result of selective attrition, natural improvement of symptoms, regression to the mean or the placebo effect (see sections 3.25 to 3.28)
- uncertainty associated with the mapping of ISI to EQ-5D (see section 3.32).

Base-case cost-effectiveness estimates

3.37 For the 50-mg dose, 12-month time horizon model, the company's preferred base-case ICER included:

- a utility mapping function using the adjusted limited dependent variable mixture model
- placebo adjustment in the no-treatment group, using the ISI score at the end of study 301 for the 12-month time horizon
- NHS prescription and outpatient costs
- the impact of adverse events on costs and QALYs.

The company disagreed with including GP training costs in its revised base case but did provide an ICER that included these. Neither the company nor

the EAG's base cases included all the committee's preferred assumptions, which were:

- the placebo effect from study 301 and study 303 (see sections 3.25 to 3.28)
- the company's utility mapping function using an adjusted limited dependent variable mixture model (see section 3.32)
- including the impact of adverse events on costs and QALYs (see section 3.31)
- including all costs that would occur in the NHS in the model (see section 3.33) and
- including the costs to provide support and training for GPs (see section 3.33).

The EAG provided an ICER that took into account the committee's preferred assumptions. This gave the committee preferred ICER of £25,383 per QALY gained.

Cost-effectiveness estimates from the company's scenario analyses

3.38 The committee also considered the following company scenarios:

- the cost effectiveness of the 25-mg dose of daridorexant
- 10% treatment effect waning and stopping treatment using an annual challenge approach in the lifetime horizon.

The committee did not make recommendations on the 25-mg dose model because the recommendations would be outside of the marketing authorisation and so outside of NICE's remit (see section 3.23). The lifetime horizon model was considered highly uncertain because the modelling assumptions were not evidence-based as there was no data beyond 12 months (see section 3.30).

The committee's preferred cost-effectiveness threshold

3.39 NICE's manual for health technology evaluations notes that judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee considered the uncertainty and the range in the cost-effectiveness estimates. It preferred an ICER threshold closer to £25,000 per QALY gained, explaining that the reason this was lower than £30,000 per QALY gained was because of the uncertainty that remained in the evidence (see section 3.36). The committee accepted that the ICER based on its preferred assumptions of £25,383 per QALY was sufficiently close to the preferred threshold of £25,000 per QALY gained. So, daridorexant was considered an acceptable use of NHS resources.

Other factors

Equality issues

3.40 The company noted that that CBTi is recommended as first-line treatment for long-term insomnia but may not be suitable for or accessible to all people. The committee recognised this and understood that care varied, with people having different standards of care for long-term insomnia depending on where they live in the country. But the committee noted that access to treatments is an implementation issue that cannot be addressed by a NICE technology appraisal recommendation. No other equality or social value issues were identified.

Innovation

3.41 The company considered that daridorexant is innovative. This is because the current medicines are recommended only for short-term use, and daridorexant is a longer-term option. Also, daridorexant is the first dual orexin receptor antagonist approved in the UK and Europe for treating long-term insomnia. The company also explained that there may be uncaptured benefits in its base-case analysis, because daridorexant may reduce the risk of cardiovascular disease and mortality in people with insomnia in the longer term. The committee concluded

that there might be additional benefits with daridorexant although these were difficult to evaluate in the lifetime horizon model. But, given the uncertainties in the evidence and in the model (see section 3.36), it was unclear whether there were any not captured in the cost-effectiveness analysis.

Conclusion

Recommendation

3.42 Clinical trial evidence shows that daridorexant improves symptoms of insomnia compared with placebo at 12 months and provides a valuable treatment option for clinicians. There is some uncertainty about its longer-term benefits compared with placebo beyond 12 months and its cost-effectiveness modelling assumptions. But, even accounting for this uncertainty, the cost-effectiveness estimates for daridorexant compared with 'no treatment' showed that the most plausible ICER was within the range NICE normally considers to be an acceptable use of NHS resources. So, daridorexant is recommended for treating long-term insomnia in adults.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has long-term insomnia and the doctor responsible for their care thinks that daridorexant is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee B.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Charles Crawley
Chair, technology appraisal committee B

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser and a project manager.

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