DERBYSHIRE JOINT AREA PRESCRIBING COMMITTEE (JAPC)

Daridorexant for treating long-term insomnia

GREY for long-term insomnia a per NICE TA922

- only if cognitive behavioural therapy for insomnia (CBTi) has been tried but not worked, or CBTi is unsuitable.
- patient with insomnia symptoms lasting for 3 nights or more per week for at least 3 months whose daytime functioning is considerably affected.

Key message

- Daridorexant is the first orexin receptor antagonist licensed in the UK for the treatment of Insomnia and is subject to 'Black Triangle' status with EU-wide additional monitoring.

- Clinical trial evidence shows that daridorexant improves symptoms of insomnia compared with placebo at month 1 & 3. Improvements seen with daridorexant 50mg in addition to placebo include
  - reduction in time to fall asleep (latency to persistent sleep, LPS) of approximately 11 minutes
  - reduction in time awake during the night (wake after sleep onset, WASO) of approximately 20 minutes
  - subjective improvements in sleep and daytime functioning

- Improvements seen with daridorexant 50mg at 3 months did not appear to persist at 12 months for some outcomes and there was no clinical data beyond 12 months.

- 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. Ongoing treatment should be reviewed regularly. The length of treatment with daridorexant should be **as short as possible** and not beyond 12 months.

- There is little to no evidence for daridorexant use in patient taking psychotropics as the main clinical trials excluded people with any mental health condition needing psychoactive medicine. Manufacturer advises caution in patients exhibiting symptoms of depression and patients with psychiatric co-morbidities.

- There is no national consensus on insomnia treatment pathway. The recommended first-line treatment is CBTi. Alternative options include hypnotic medicines, such as benzodiazepines, non-benzodiazepine GABA-A receptor agonists (referred to as ‘z-drugs’ such as zolpidem), melatonin, and off-label sedating antidepressants and antihistamines. There is no direct or indirect evidence comparing daridorexant to these treatments.

- The studies provide evidence in patients who do not have access to CBT-I but provide minimal evidence in patients who have failed CBT-I.

- The European regulatory review noted a potential abuse concern with daridorexant, but no evidence of a withdrawal syndrome on abrupt discontinuation.

Background
Insomnia is difficulty in getting to sleep, difficulty maintaining sleep, early wakening, or non-restorative sleep which occurs despite adequate opportunity for sleep and results in impaired daytime functioning. Daytime symptoms typically include poor concentration, mood disturbance, and fatigue. Sleep disturbance in the absence of daytime impairment is not considered to be insomnia disorder.

Insomnia symptoms occurring on at least 3 nights per week for three months or more is referred to as chronic or long-term insomnia. [CKS]

Treatment for long-term insomnia [BMJ best practice/ CKS]
Take an individualised approach to treatment, based on the patient's preferences, the severity of their insomnia, the risks versus benefits of treatment.

Identify underlying condition/ triggers
Identify and optimise management of any underlying medical condition (e.g., chronic pain, hot flushes, obstructive sleep apnoea) or psychiatric disorders (e.g., depression) that may be contributing to the ongoing sleep disturbance. Address any triggers or factors associated with maintenance of insomnia.

Review the patient's usual medications to establish whether they include drugs that may cause or worsen insomnia, such as stimulants, antidepressants, corticosteroids, or diuretics; if so, consider whether it is possible to lower the dosage and/or give the medicine earlier in the day.

Advise on sleep hygiene and relaxation techniques
- Normal sleep and changes in sleep patterns with age
- Sleep environment
- Regular sleep schedules
- Relaxation before going to bed
- Limiting/avoidance of caffeine, nicotine and alcohol
- Exercise

Cognitive behavioural therapy for insomnia (CBTi)
CBTi is the standard first treatment for people with long-term insomnia after sleep hygiene advice is offered.
Sleepio website or App is one of the digital tool for patients in England.

Pharmacological treatment
Avoid pharmacological therapy in the long-term management of insomnia if possible.
CKS suggests the following options may be considered
- short course of a hypnotic drug (preferably less than 1 week) in severe symptoms or acute exacerbation, as a temporary adjunct to behavioural and cognitive treatment. Do not prescribe long-term hypnotic treatment
- prolonged-release melatonin for people over 55 years of age with persistent insomnia (maximum duration 13 weeks). Locally classified as Grey not recommended except in exceptional circumstances.
- daridorexant for adults with chronic insomnia whose daytime functioning is considerably affected, only if CBTi has been tried but not worked, or is unavailable or unsuitable.

Daridorexant prescribing information

Before Starting

- confirm diagnosis of chronic insomnia
- identify/address underlying condition/ triggers
- give sleep hygiene advice and relaxation techniques
- consider CBTi [e.g. access via https://sleepio.com/sleepio/nhs/391#1/1]
- confirm patient meets NICE TA922 criteria

Dosages & administration

50mg once per night, taken orally in the evening within 30 minutes prior to going to bed. Reduce to 25mg in those with moderate hepatic dysfunction or when taking CYP3A4 inhibitors. Taking daridorexant soon after a large meal may reduce the effect of sleep onset. The consumption of grapefruit or grapefruit juice in the evening should be avoided.

Review & follow up

The length of treatment should be as short as possible. When initiating treatment with daridorexant, treatment expectations, requirements for review and trials without medication should be outlined. **Assess treatment within 3 months of starting**. Stop treatment in people who have not responded adequately.

If treatment is continued, assess whether it is still working at regular intervals. (e.g. every 3-6 months). Lifestyle factors should be addressed at each review. Clinical data is available for up to 12 months of continuous treatment. Treatment can be stopped without down-titration.

The safety profile of daridorexant is characterised by mainly mild to moderate adverse effects, with small increases, compared with placebo, in headache, somnolence, fatigue, dizziness and nausea.

Contraindications and precautions (see SPC for full detail)

- narcolepsy
- concomitant use with strong CYP3A4 inhibitors
- elderly- limited data is available in those >75 years and no data >85 years.
- psychiatric co-morbidities- in primarily depressed patients treated with hypnotics, worsening of depression and suicidal thoughts and actions have been reported.
- severe obstructive sleep apnoea & severe COPD- lack of data in these patients
- individuals with a history of abuse or addiction to alcohol or other substances may be at increased risk for abuse of daridorexant.
- pregnancy/ lactation- lack of data, seek specialist advice.

Information and support

NHS - insomnia

Mental Health Foundation Insomnia- How to sleep better

Royal College of Psychiatrists – Sleeping well

Organisations

- The Sleep Charity
- The British Sleep Society

References:

NICE TA922 Daridorexant for treating long-term insomnia published 19 Oct 2023. https://www.nice.org.uk/guidance/ta922

NICE CKS insomnia, last revised May 2022. https://cks.nice.org.uk/topics/insomnia/ accessed 15/3/2024

BMJ best practice

QUVIVIQ Summary of Product characteristics. Last updated 25th October 2023. Accessed via MHRA Products | Home.