NICE advice

Narcolepsy with or without cataplexy in adults: pitolisant

Evidence summary
Published: 14 March 2017

www.nice.org.uk/guidance/es8

Key points

The content of this evidence summary was up-to-date in March 2017. See summaries of product characteristics (SPC), British national formulary (BNF) or the MHRA or NICE websites for up-to-date information.

Regulatory status: New medicine. Pitolisant is a histamine H3-receptor antagonist/inverse agonist that is licensed for the treatment of narcolepsy with or without cataplexy in adults. It was launched in the UK in September 2016.

Overview

Narcolepsy is a rare, disabling long-term brain disorder that can result in excessive daytime sleepiness, sleep attacks, cataplexy, sleep paralysis, excessive dreaming and disturbed nocturnal sleep.

This evidence summary reviewed 2 small randomised controlled trials (RCTs) of pitolisant 5–40 mg per day in adults with narcolepsy with or without cataplexy. Compared with

placebo, pitolisant improved excessive daytime sleepiness, improved time awake in a darkened room and reduced the weekly cataplexy rate. Pitolisant was also compared with modafinil in a non-inferiority analysis (an analysis designed to test if it was not worse than modafinil for improving excessive daytime sleepiness by a pre-specified amount). Non-inferiority to modafinil was not shown.

The long-term safety data for pitolisant in people with narcolepsy are limited. Narcolepsy is an orphan disease, and clinical studies included small numbers of people for a short duration of time. In the 2 RCTs reviewed in this evidence summary, the most common adverse events in the pitolisant groups were headache, insomnia, abdominal discomfort, nausea, irritability and anxiety. No participants in the pitolisant groups had withdrawal syndrome during the withdrawal phase.

Pitolisant is the first of a new class of medicine licensed to treat narcolepsy with or without cataplexy, and is an additional option that could be used in this rare condition. Other medicines licensed for use in narcolepsy include the central nervous system stimulants, modafinil and dexamfetamine, and the central nervous system depressant, sodium oxybate.

A summary to inform local decision-making is shown in table 1.

Table 1 Summary of the evidence on effectiveness, safety, patient factors and resource implications

Effectiveness

- Pitolisant 10 mg to 40 mg per day[a] was statistically and clinically superior to placebo for improving excessive daytime sleepiness measured by the Epworth Sleepiness Scale (ESS). The mean difference was −3.0 points; 95% confidence interval (CI) −5.6 to −0.4, p=0.024 (HARMONY I [Dauvilliers et al. 2013], 8-week duration, n=95).
- Pitolisant 10 mg to 40 mg per day[a] was not shown to be non-inferior to modafinil 100 mg to 400 mg per day for excessive daytime sleepiness measured by the ESS. The mean difference was 0.12 points; 95% CI −2.5 to 2.7, p=0.250, which was outside the non-inferiority margin of 2 points (HARMONY I, 8-week duration, n=95).
- For time awake in a darkened room, pitolisant 10–40 mg per day[a] was statistically superior to placebo by a factor of 1.47 (95% CI 1.01 to 2.14, p=0.044) and there was no statistically significant difference compared with modafinil 100 mg to 400 mg per day (0.77; 95% CI 0.52 to 1.13, p=0.173) measured by the maintenance of wakefulness test. There was an increase from a baseline of 7.4 minutes to 9.7 minutes in the pitolisant group, and 8.8 minutes to 15.1 minutes in the modafinil group (HARMONY I, 8-week duration, n=95).
- For attention level, there was no statistically significant difference between pitolisant 10 mg to 40 mg per day[a] and placebo, or pitolisant 10 mg to 40 mg per day[a] and modafinil 100 mg to 400 mg per day for the sustained attention to response task total score (HARMONY I, 8-week duration, n=95).
- Pitolisant 5 mg to 40 mg per day[a] reduced the weekly cataplexy rate by about half compared with placebo (rate ratio 0.51; 95% CI 0.44 to 0.60, p<0.0001); from a baseline of 9.15 to 2.27 attacks per week in the pitolisant group, and 7.31 to 4.52 attacks per week in the placebo group (HARMONY-CTP [Szakacs et al. 2017], 7-week duration, n=106).

Safety

- Pitolisant is contraindicated in severe hepatic impairment and should be administered with caution in people with moderate hepatic impairment or renal impairment, a history of psychiatric disorders, acid related gastric disorders or taking concomitant gastric irritants, severe obesity or anorexia, severe epilepsy, cardiac disease, taking concomitant QT-prolonging medicines or CYP2D6 inhibitors (pitolisant summary of product characteristics [SPC]).
- Women of childbearing potential have to use effective contraception during treatment and for at least 21 days after discontinuation. Pitolisant may reduce the effectiveness of hormonal contraceptives and alternative methods of contraceptives should be used (pitolisant SPC).
- The most serious adverse drug reactions are abnormal weight decrease (0.09%) and spontaneous abortion (0.09%; pitolisant SPC).

Patient factors

- Pitolisant tablets should be used at the lowest effective dose, depending on individual response and tolerance (dose range 4.5 mg to 36 mg per day[a]). It is estimated that about one third of people will be maintained on 18 mg per day and two thirds of people will require 36 mg per day.
- Pitolisant is taken as a single dose in the morning during breakfast.
- The most frequent adverse drug reactions are insomnia (8.4%), headache (7.7%), nausea (4.8%), anxiety (2.1%), irritability (1.8%), dizziness (1.4%), depression (1.3%), tremor (1.2%), sleep disorders (1.1%), fatigue (1.1%), vomiting (1.0%), vertigo (1.0%), dyspepsia (1.0%), weight increase (0.9%), and upper abdominal pain (0.9%; pitolisant SPC).

Resource implications

- The cost of 30 days treatment with pitolisant at a dose of 4.5 mg to 36 mg once daily is £310.00 to £620.00 (MIMS, February 2017, excluding VAT).
- The cost of 30 days treatment with other medicines used for narcolepsy is £6.06 to £318.24 for stimulants such as modafinil, dexamfetamine or methylphenidate and £540.00 to £1,080.00 for sodium oxybate (Drug Tariff, February 2017, excluding VAT).

[a] In the RCTs, pitolisant was given as pitolisant hydrochloride 5 mg to 40 mg, which is equivalent to a pitolisant dose of 4.5 mg to 36 mg.

Introduction and current guidance

Narcolepsy is a rare, disabling long-term brain disorder that causes a person to fall asleep at inappropriate times. It is estimated to affect at least 25,000 people in the UK, and is usually diagnosed between 20 and 40 years of age, although the symptoms often begin during adolescence (Narcolepsy: NHS Choices).

In people with narcolepsy, the brain is unable to regulate sleep and waking patterns normally, which can result in:

- excessive daytime sleepiness: feeling very sleepy throughout the day, and having difficulty concentrating and staying awake
- sleep attacks: falling asleep suddenly and without warning
- cataplexy: temporary loss of muscle control resulting in weakness and possible collapse, often in response to emotions such as laughter and anger
- sleep paralysis: a temporary inability to move or speak when waking up or falling asleep
- excessive dreaming: dreams often come when falling asleep (hypnogogic hallucinations) or just before or during waking (hypnopompic hallucinations)
- disturbed nocturnal sleep: frequent waking in the night.

Managing narcolepsy involves implementing good sleep hygiene, which may include taking

brief planned naps and sticking to a strict bedtime routine. Accessing counselling and support may also be important for people to come to terms with the sleep disorder and its implications. Several medicines are used to treat the symptoms of narcolepsy. These include stimulants such as modafinil, dexamfetamine or methylphenidate; sodium oxybate; or antidepressants such as selective serotonin reuptake inhibitors (SSRIs), serotonin–noradrenaline reuptake inhibitors (SNRIs) or tricyclic antidepressants. Many of these medicines are not licensed for the treatment of narcolepsy and they vary in the evidence available for their effectiveness in treating narcolepsy. See Narcolepsy: NHS Choices and the EFNS guidelines on management of narcolepsy (Billiard et al. 2006) for more details.

Product overview

Mode of action

Pitolisant is a potent, orally active histamine H3-receptor antagonist/inverse agonist. It blocks histamine auto-receptors enhancing the activity of brain histaminergic neurons, a major arousal system with widespread projections to the whole brain. Pitolisant also modulates various neurotransmitter systems, increasing acetylcholine, noradrenaline and dopamine release in the brain (pitolisant summary of product characteristics [SPC]).

Regulatory status

Pitolisant (Wakix: Lincoln Medical Limited) received a marketing authorisation from the European Medicines Agency (EMA) in March 2016 for the treatment of narcolepsy with or without cataplexy in adults. In April 2016, the EMA recommended that its status as an orphan medicinal product should also be maintained. Pitolisant was launched in the UK in September 2016.

Dosing information

Pitolisant is available as 4.5 mg tablets (which contain 5 mg of pitolisant hydrochloride equivalent to 4.5 mg of pitolisant) and 18 mg tablets (which contain 20 mg of pitolisant hydrochloride equivalent to 18 mg of pitolisant). Treatment should be initiated by a clinician experienced in the treatment of sleep disorders. Pitolisant should be used at the lowest effective dose, depending on individual response and tolerance, without exceeding

36 mg per day (pitolisant SPC).

It should be titrated as follows:

- Week 1: initial dose of 9 mg (2×4.5 mg tablets) per day.
- Week 2: the dose may be increased to 18 mg (1×18 mg tablet) per day or decreased to 4.5 mg (1×4.5 mg tablet) per day.
- Week 3: the dose may be increased to 36 mg (2×18 mg tablets) per day.

At any time the dose can be decreased (down to 4.5 mg per day) or increased progressively (up to 36 mg per day) according to response. The total daily dose should be given as a single dose in the morning during breakfast.

The company estimate that approximately one third of people will be maintained on 18 mg per day and two thirds of people will require 36 mg per day (source: Lincoln Medical Ltd, October 2016).

The summary of product characteristics states that long-term efficacy data are limited and the continued efficacy of pitolisant should be regularly evaluated.

Limited data are available in older people, and dosing should be adjusted according to their renal and hepatic status. In people with renal impairment, the maximum daily dose is 18 mg. In people with mild hepatic impairment no dosage adjustment is required. In people with moderate hepatic impairment, 2 weeks after treatment is started, the daily dose can be increased but only to a maximum daily dose of 18 mg. Pitolisant is contraindicated in people with severe hepatic impairment.

The safety and efficacy of pitolisant in children up to 18 years of age has not been established.

Cost

Pitolisant 4.5 mg tablets and pitolisant 18 mg tablets cost £310.00 for 30 tablets excluding VAT (MIMS, February 2017).

Evidence review

A literature search was conducted which identified 34 references (see search strategy for full details). These references were screened using their titles and abstracts and 3 references were obtained and assessed for relevance.

One randomised controlled trial (RCT) identified from the search (Dauvilliers et al. 2013; HARMONY I) was included in this evidence summary. An additional RCT (Szakacs et al. 2017; HARMONY-CTP) which was considered by the European Medicines Agency during the regulatory process and was published after the search was conducted was also included. A summary of the included studies is shown in table 2 (see evidence tables for full details).

The remaining 2 references were excluded. These are listed in excluded studies with reasons for their exclusion.

The European Public Assessment Report (EPAR) for pitolisant states that the narcolepsy development programme included 5 phase III trials, of which HARMONY I and HARMONY Ibis (unpublished) were considered pivotal for the indication in the treatment of narcolepsy with or without cataplexy. See excluded studies for details.

Table 2 Summary of included studies

Study	Population	Intervention and comparison	Primary outcome

Dauvilliers et al. 2013 (HARMONY I) RCT	Adults with narcolepsy with or without cataplexy (n=95)	Pitolisant 10 mg, 20 mg or 40 mg per day[a] versus modafinil 100 mg, 200 mg or 400 mg per day versus placebo	Difference in change in ESS score • between pitolisant and placebo (to demonstrate superiority) • between pitolisant and modafinil (to demonstrate non-inferiority)
Szakacs et al. 2017 (HARMONY-CTP) RCT	Adults with narcolepsy with cataplexy (n=106)	Pitolisant 5 mg, 10 mg, 20 mg or 40 mg per day[b] versus placebo	Weekly cataplexy rate change between pitolisant and placebo
Abbreviations: ESS, Epworth Sleepiness Scale; RCT, randomised controlled trial [a] as pitolisant hydrochloride; equivalent to 9 mg, 18 mg or 36 mg per day of pitolisant [b] as pitolisant hydrochloride; equivalent to 4.5 mg, 9 mg, 18 mg or 36 mg per day of pitolisant			

Clinical effectiveness

This evidence summary is based on 2 double-blind RCTs.

The first 8-week RCT compared pitolisant with modafinil or placebo in 95 adults with narcolepsy with or without cataplexy; 81% had a history of cataplexy (HARMONY I; Dauvilliers et al. 2013). Participants had to have an Epworth Sleepiness Scale score of 14 or more (mean baseline score was about 18) and were withdrawn from any previous psychostimulants (45% had taken these previously). Participants could remain on sodium oxybate or non-tricyclic antidepressants at stable doses (35% remained on these). See evidence tables for details.

Pitolisant (as hydrochloride) was given at a flexible dose of 10 mg, 20 mg or 40 mg per day (equivalent to 9 mg, 18 mg or 36 mg per day of pitolisant) for 3 weeks, followed by 5 weeks of stable dosing. Modafinil was given at a flexible dose of 100 mg, 200 mg or 400 mg per day for 3 weeks, then again at a stable dose for 5 weeks. Following the 8-week treatment phase all participants received placebo for 1 week (the withdrawal phase). During the stable dose phase of the trial, 61% of participants were taking pitolisant 40 mg per day, 26% were taking 20 mg per day and 7% were taking 10 mg per day. In the modafinil treatment arm, 73% were taking 400 mg per day, 12% were taking 200 mg per day and 6% were taking 100 mg per day (EPAR for pitolisant).

The second 7-week RCT compared pitolisant with placebo in 106 adults with a diagnosis of narcolepsy with cataplexy (HARMONY-CTP; Szakacs et al. 2017). Participants had to have 3 or more cataplexy attacks per week (mean baseline was 11 per week in the pitolisant group and 9 per week in the placebo group) and an Epworth Sleepiness Scale score of 12 or more (mean baseline score was 17 in both groups). Any previous psychostimulants were withdrawn, but participants could remain on sodium oxybate or antidepressants at stable doses for cataplexy. In the pitolisant group, 41% of people were taking cataplexy medication before the trial and 7% continued with this throughout the trial. In the placebo group, 80% of people were taking cataplexy medication before the trial and 16% continued this. See evidence tables for details. Pitolisant (as hydrochloride) was given at a flexible dose of 5 mg, 10 mg or 20 mg per day (equivalent to 4.5 mg, 9 mg or 18 mg per day of pitolisant) for 3 weeks, followed by 4 weeks of stable dosing at 5 mg, 10 mg, 20 mg or 40 mg per day. Following the 7-week treatment phase all participants received placebo for 1 week (the withdrawal phase). During the stable dose phase of the trial, 35 participants were taking pitolisant 40 mg per day, 9 participants were taking 20 mg per day and 7 participants were taking 10 mg per day.

Excessive daytime sleepiness

The primary outcome of HARMONY I was the difference in change in excessive daytime sleepiness measured by the Epworth Sleepiness Scale (ESS). This is a subjective, self-administered questionnaire which assesses how likely people are to doze off or fall asleep in life situations, such as watching television. The maximum score on this scale is 24 (with higher scores indicating more chance of dozing off) and the minimum clinically important difference is 3 points.

After 8 weeks of treatment, pitolisant was statistically and clinically superior to placebo for the change from baseline in ESS score in the intention-to-treat population. There was a

mean decrease of 5.8 points from a baseline of 17.8 points in the pitolisant group compared with a mean decrease of 3.4 points from a baseline of 18.9 points in the placebo group. When adjusted for baseline, the mean difference was −3.0 points (95% confidence interval [CI] −5.6 to −0.4, p=0.024) in favour of pitolisant.

Pitolisant was also compared with modafinil in HARMONY I using a non-inferiority analysis. This was an analysis designed to test if pitolisant was at least not worse than modafinil for improving excessive daytime sleepiness by a pre-specified non-inferiority margin of 2 points on the ESS score. There was a mean decrease of 5.8 points from a baseline of 17.8 points in the pitolisant group compared with a mean decrease of 6.9 points from a baseline of 18.5 points in the modafinil group. When adjusted for baseline, the mean difference was 0.12 (95% CI −2.5 to 2.7, p=0.250) with pitolisant compared with modafinil. This was outside the pre-specified non-inferiority margin of 2 points, therefore non-inferiority was not shown. This finding was confirmed in the per-protocol population.

The proportion of people who had improvement in excessive daytime sleepiness assessed by modified clinical global impression of change (CGI-C) was 56% (14/25) in the placebo group, 73% (19/26) in the pitolisant group and 86% (24/28) in the modafinil group (no analysis reported).

Secondary end points in HARMONY I included changes on the maintenance of wakefulness test (MWT) and sustained attention to response task (SART). These are objective laboratory-based assessments of time awake in a darkened room and attention level respectively.

For the MWT, pitolisant was statistically superior to placebo by a factor of 1.47 (95% CI 1.01 to 2.14, p=0.044) and there was no statistically significant difference compared with modafinil (0.77; 95% CI 0.52 to 1.13, p=0.173). Time awake in a darkened room increased from a baseline of 7.4 minutes to 9.7 minutes in the pitolisant group and from a baseline of 8.8 minutes to 15.1 minutes in the modafinil group after 8 weeks of treatment.

For attention level, there was no statistically significant difference between pitolisant and placebo, or pitolisant and modafinil, for SART-total scores. European quality of life questionnaire (EQ-5D) values were similar in all 3 groups. See results tables for details.

The effects of pitolisant on excessive daytime sleepiness were secondary end points in HARMONY-CTP. After 7 weeks of treatment, pitolisant was statistically and clinically superior to placebo for the change from baseline in ESS score. There was a mean

decrease of 5.4 points from a baseline of 17.4 points in the pitolisant group compared with a mean decrease of 1.9 points from a baseline of 17.3 points in the placebo group. When adjusted for baseline, the difference was −3.48 points (95% CI −5.03 to −1.92, p=0.0001) in favour of pitolisant. For the MWT, pitolisant was statistically superior to placebo by a factor of 1.85 (95% CI 1.24 to 2.74, p=0.003). Time awake in a darkened room increased from a baseline of 3.5 minutes to 6.9 minutes in the pitolisant group. See results tables for details.

Cataplexy

At baseline, 81% of participants in HARMONY I had a history of cataplexy and 61% were considered still to have cataplexy during the trial, reporting 1 or more cataplexy episodes. There was little between-group differences in the change in severity of cataplexy assessed by CGI-C. The proportion of people who had improvement was 24% (6/25) in the placebo group, 35% (9/26) in the pitolisant group and 29% (8/28) in the modafinil group (no analysis reported).

Assessing the effect of pitolisant on cataplexy was the main objective of the HARMONY-CTP study. The primary outcome was the change in weekly cataplexy rate between pitolisant and placebo, based on the change in the average number of cataplexy attacks per week between the 2 weeks of baseline and the 4 weeks of stable dosing in each group. After 7 weeks of treatment, pitolisant was statistically superior to placebo in the intention-to-treat population. The mean weekly cataplexy rate reduced by 75% (from 9.15 to 2.27 attacks per week) in the pitolisant group and by 38% (from 7.31 to 4.52 attacks per week) in the placebo group; a rate ratio of 0.51 (95% CI 0.44 to 0.60, p<0.0001) with pitolisant compared with placebo.

An overview of the results for clinical effectiveness can be found in results tables.

Safety and tolerability

Pitolisant is contraindicated in people with severe hepatic impairment and should be administered with caution in people with moderate hepatic impairment or renal impairment, with the dosing regimen adapted (see dosing information; pitolisant summary of product characteristics [SPC]).

Pitolisant should be administered with caution in people with a history of psychiatric disorders (such as severe anxiety or severe depression with suicidal ideation risk); in

people with acid-related gastric disorders or when co-administered with gastric irritants (such as corticosteroids or NSAIDs); in people with severe obesity or severe anorexia; and in people with severe epilepsy. There is a risk of mild to moderate prolongation of QTc interval with supra-therapeutic doses of pitolisant, therefore caution and monitoring is required in people with cardiac disease; those taking other QT-prolonging medicines; those taking medicines that are known to increase pitolisant levels (for example CYP2D6 inhibitors, such as paroxetine); or people with severe renal or moderate hepatic impairment. No rebound effect was reported during clinical trials of pitolisant but treatment discontinuation should be monitored. See the pitolisant SPC for details.

Women of childbearing potential have to use effective contraception during treatment and for at least 21 days after treatment discontinuation. Pitolisant may reduce the effectiveness of hormonal contraceptives, therefore an alternative method of effective contraception should be used. Pitolisant may induce CYP3A4 and CYP2B6 enzymes, therefore its use with substrates of these that have a narrow therapeutic margin should be avoided. Pitolisant levels may also be decreased when it is co-administered with potent CYP3A4 inducers (pitolisant SPC).

The most frequent adverse drug reactions reported in the pitolisant SPC are insomnia (8.4%), headache (7.7%), nausea (4.8%), anxiety (2.1%), irritability (1.8%), dizziness (1.4%), depression (1.3%), tremor (1.2%), sleep disorders (1.1%), fatigue (1.1%), vomiting (1.0%), vertigo (1.0%), dyspepsia (1.0%), weight increase (0.9%), and upper abdominal pain (0.9%). The most serious adverse drug reactions are abnormal weight decrease (0.09%) and spontaneous abortion (0.09%).

The EPAR discusses that the long-term safety data for pitolisant in people with narcolepsy are limited. In HARMONY III (NCT01399606) an unpublished open-label, 12-month safety study, only 10 people received a 20 mg daily dose and 87 people received a 40 mg daily dose. As narcolepsy is an orphan disease, clinical studies include small numbers of people and their ability to detect rare adverse reactions or adverse reactions due to prolonged exposure is low. The EPAR states that some uncertainties remain with regard to the effects of pitolisant on depression, weight and appetite, ulcer formation, and more generally on adverse events that might occur after long-term exposure.

An overview of the results for the safety and tolerability of pitolisant in HARMONY I and HARMONY-CTP can be found in the results tables.

In HARMONY I, adverse events occurred in 71% (22/31) of the pitolisant group, 79% (26/

33) of the modafinil group and 33% (10/30) of the placebo group. The most frequent adverse events were headache for all 3 groups; insomnia, abdominal discomfort and nausea for the pitolisant group; and abdominal discomfort, nausea, diarrhoea, dizziness, anxiety and irritability for the modafinil group. Serious adverse events occurred in 1 person in the pitolisant group (abdominal pain), 5 people in the modafinil group (1 case each of abdominal pain, abnormal behaviour, withdrawal symptoms, lymphoadenopathy and inner ear disorder), and no people in the placebo group. No participants in the placebo or pitolisant group had withdrawal syndrome during the withdrawal phase, compared with 3 participants in the modafinil group.

In HARMONY-CTP, adverse events occurred in 35% (19/54) of the pitolisant group and 31% (16/51) of the placebo group (p=0.528). These were considered treatment related in 28% (15/54) of the pitolisant group and 12% (6/51) of the placebo group (p=0.048). The most frequent adverse events were headache for both groups; irritability, anxiety and nausea for the pitolisant group; and somnolence for the placebo group. Severe adverse events occurred in 1 person in the pitolisant group (nausea) and no people in the placebo group. No participants in the pitolisant group had withdrawal syndrome during the withdrawal phase, compared with 1 participant in the placebo group.

Evidence strengths and limitations

An overview of the quality assessment of the included studies HARMONY I (Dauvilliers et al. 2013) and HARMONY-CTP (Szakacs et al. 2017) can be found in the evidence tables. These RCTs had several limitations including small patient numbers (n=95 and n=106) and a short duration (8-week or 7-week treatment phase), which limits findings related to long-term efficacy and safety in particular. The authors of both studies state that flexible dosage and multiple visits could have affected efficacy, with less responsive people being titrated to the highest dose. There is also a concern about the limited generalisability of the findings because children, those with unstable comorbidities, and those who declined to participate because they didn't want to receive placebo were excluded. In both studies, people had to discontinue psychostimulants before baseline, but could remain on stable doses of sodium oxybate or antidepressants for treating cataplexy. About 35% of people continued on these medicines in HARMONY I; and 7% (in the pitolisant group) and 16% (in the placebo group) in HARMONY-CTP, therefore the findings may not be generalisable to people who are not taking any other medicines for narcolepsy or cataplexy.

The method of randomisation in the double-blind RCTs suggests allocation was concealed and a double-dummy design was used to ensure HARMONY I remained double-blind.

However, people who had received modafinil before in HARMONY I (between 33% and 43% of participants) may have realised they were taking it because of its effects.

HARMONY I was designed to assess the superiority of pitolisant compared with placebo, and the non-inferiority of pitolisant compared with modafinil. However, the EPAR states that the trial protocol was amended from an original design to assess the superiority of pitolisant compared with modafinil.

The primary outcome of HARMONY I was the change in excessive daytime sleepiness measured by the Epworth Sleepiness Scale. This is a subjective, self-administered questionnaire, but it is widely used in narcolepsy trials, and the EPAR states it is suitable when combined with an objective secondary end point such as the maintenance of wakefulness test. Another of the secondary end points, the modified CGI-C is a non-validated measure in narcolepsy. The occurrence of withdrawal syndrome after treatment ended was assessed, but the authors state that early withdrawal effects might have been missed if they were not recalled or reported by participants and if the scale used was not sensitive enough.

The primary outcome of HARMONY-CTP was the change in weekly cataplexy rate, as reported in patient diaries. Participants were asked to report all cataplexy attacks defined as sudden and transient episodes (ranging from several seconds to a few minutes) of partial or generalised loss of muscle tone triggered by emotion. A high placebo effect was found on cataplexy rate reduction, which might reflect subjective and emotional triggers.

The authors of HARMONY-CTP state that baseline characteristics were similar in the 2 groups. However, there were numerical differences in the mean number of cataplexy episodes per week (11 in the pitolisant group; 9 in the placebo group) and proportion of people who had taken cataplexy medicines in the previous 3 months (41% in the pitolisant group at baseline with 7% continuing during the trial; 80% in the placebo group at baseline with 16% continuing during the trial); no analysis reported.

A commentary accompanying the publication of HARMONY-CTP (Baumann 2017) suggests the main limitation of this study was the use of non-specific criteria for the diagnosis of narcolepsy. This limitation would also apply to HARMONY I. In both RCTs, narcolepsy was diagnosed using the International Classification of Sleep Disorders-2 (ICSD-2), rather than the more recent ICDS-3, because the trials were started before this was published. See Sateia 2014 for more information on diagnostic criteria.

This evidence summary is based on HARMONY I and HARMONY-CTP because these studies have been published. However, the EPAR for pitolisant states that HARMONY I and the unpublished study HARMONY Ibis were considered pivotal for the indication in the treatment of narcolepsy with or without cataplexy.

According to the EPAR, HARMONY Ibis was an RCT with a similar trial design to HARMONY I, with an 8-week treatment phase and a 1-week withdrawal phase. However, the dose of pitolisant was lower at a range of 5 mg to 20 mg per day rather than 10 mg to 40 mg per day. In HARMONY Ibis, 166 people were randomised to either placebo (n=33), pitolisant 5 mg to 20 mg per day (n=67) or modafinil 100 mg to 400 mg per day (n=66). For the primary outcome, the change in excessive daytime sleepiness measured by the Epworth Sleepiness Scale, pitolisant was not superior to placebo (mean difference −1.94 points; 95% CI −4.05 to 0.07, p=0.065). There was a mean decrease of 4.6 points from a baseline of 18.3 points in the pitolisant group, a mean decrease of 3.6 points from a baseline of 18.2 points in the placebo group and a mean decrease of 7.8 points from baseline of 18.1 points in the modafinil group.

When non-inferiority compared with modafinil was considered, pitolisant was not established as non-inferior to modafinil based on the pre-specified non-inferiority margin of −2 points (mean difference −2.75 points; 95% CI −4.48 to −1.02). The EPAR states that HARMONY Ibis was most likely underpowered, and the low dose may not have been sufficient for many people. In HARMONY I, 61% of participants were taking pitolisant 40 mg per day during the stable dose phase of the trial.

Estimated impact for the NHS

Other treatments

Managing narcolepsy involves implementing good sleep hygiene and accessing counselling and support. Medicines used to treat the symptoms of narcolepsy include stimulants such as modafinil, dexamfetamine or methylphenidate (off-label), and sodium oxybate. Antidepressants such as selective serotonin reuptake inhibitors (SSRIs; for example fluoxetine), serotonin-noradrenaline reuptake inhibitors (SNRIs; for example venlafaxine) or tricyclic antidepressants (for example clomipramine) are also used off-label (Narcolepsy: NHS Choices).

Costs of other medicines

See table 3 for details.

Table 3 Costs of other medicines used in narcolepsy: stimulants and sodium oxybate

Medicine	Usual dose[a]	Cost per 30 days treatment, excluding VAT
Pitolisant tablets	4.5 mg to 36 mg once daily[b]	£310.00 to £620.00[c]
Modafinil tablets	Initially 200 mg (elderly 100 mg) daily, either in 2 divided doses morning and at noon or as a single dose in the morning, adjusted according to response to 200 mg to 400 mg daily in 2 divided doses or as a single dose[d]	£6.59 to £32.38[e]
Methylphenidate tablets	10 mg to 60 mg (usually 20 mg to 30 mg) daily in divided doses before meals[f]	£6.06 to £32.76[e]
Dexamfetamine tablets	Initially 10 mg (elderly 5 mg) daily in divided doses increased at weekly intervals by 10 mg (elderly 5 mg) daily to a maximum of 60 mg daily[g]	£26.52 to £318.24[e]
Sodium oxybate oral solution 500 mg/ml	Initially 2.25 g on retiring and repeated 2.5 to 4 hours later, increased according to response in steps of 1.5 g daily in 2 divided doses at intervals of 1 to 2 weeks to a maximum of 9 g daily in 2 divided doses[h]	£540.00 to £1,080.00[e,i]

[a] These directions do not represent the full range that can be used and they do not imply therapeutic equivalence.

[b] From pitolisant summary of product characteristics. Pitolisant is licensed in adults for the treatment of narcolepsy with or without cataplexy.

[c] Costs taken from MIMS, February 2017 (excluding VAT).

[d] From BNF and modafinil summary of product characteristics. Modafinil is licensed in adults for the treatment of excessive sleepiness associated with narcolepsy with or without cataplexy.

[e] Costs taken from Drug Tariff, February 2017 (excluding VAT).

[f] From BNF. Methylphenidate is not licensed for narcolepsy (methylphenidate summaries of product characteristics).

[g] From BNF and dexamfetamine summaries of product characteristics. Dexamfetamine is licensed for narcolepsy.

[h] From BNF and sodium oxybate summary of product characteristics. Sodium oxybate is licensed in adults for the treatment of narcolepsy with cataplexy.

[i] Lower cost estimate is based on the exact cost for the volume required (270 ml) for a 30-day supply at a dose of 4.5 g daily. However sodium oxybate is a special container with a pack size of 180 ml, therefore the pack cannot be split. In practice the prescribed quantity would need to be a multiple of 180 ml, taking into account that sodium oxybate is a schedule 2 controlled drug and the quantity prescribed should be enough meet the person's clinical needs for no more than 30 days (Drug Tariff, February 2017; NICE guideline on Controlled drugs: safe use and management).

Current or estimated usage

The company anticipate that pitolisant will be used initially for people with narcolepsy who either cannot tolerate current treatments or have not responded to these. They estimate that there are approximately 30,000 people in the UK with narcolepsy, about 5,000 of who receive medicines to treat this. Of these, they estimate that about 50% of people who are currently being treated may have issues with their existing medicines and may be eligible for treatment with pitolisant; equating to 2,500 people over a 5-year period (source: Lincoln Medical Ltd, October 2016).

Likely place in therapy

Pitolisant is the first of a new class of medicine, a histamine H3-receptor antagonist/inverse agonist, licensed to treat narcolepsy. The European Public Assessment Report (EPAR) concluded that there is sufficient evidence supporting pitolisant efficacy in the treatment of narcolepsy with or without cataplexy in adults and the safety profile is acceptable in this condition, although further long-term safety data are required.

Pitolisant is an additional class of medicine that could be used to treat narcolepsy with or without cataplexy. Other medicines licensed for use in this rare condition include the central nervous system stimulants, modafinil and dexamfetamine, and the central nervous system depressant, sodium oxybate. The EPAR suggests that modafinil is the first-line treatment for excessive daytime sleepiness in people with narcolepsy, but its effect on cataplexy is less clear. However, modafinil and other stimulants can have serious cardiovascular and central nervous system side effects (including hypertension, tachycardia, anxiety and depression) and could lead to abuse disorders and weight loss. The summary of product characteristics (SPC) for modafinil states that while studies have demonstrated a low potential for dependence, the possibility of dependence with long-term use cannot be entirely excluded, and caution is needed in people with a history of alcohol, drug or illicit substance abuse. Further information to support the safe use of modafinil is available in a Drug Safety Update from 2011.

Sodium oxybate is used in particular to treat cataplexy, but it has abuse potential. The SPC for sodium oxybate states that there is no clear evidence of dependence at therapeutic doses, but this possibility cannot be excluded because of reports of dependence after illicit use at frequent repeated doses in excess of the therapeutic dose range. Sodium oxybate is a schedule 2 controlled drug with requirements around supply, possession, prescribing, and record keeping.

In the limited number of clinical trials that are available with pitolisant in narcolepsy, the most frequent adverse drug reactions reported were insomnia, headache, nausea, anxiety, irritability, dizziness, depression, tremor, sleep disorders, fatigue, vomiting, vertigo, dyspepsia, weight increase, and upper abdominal pain. No rebound effects were seen but the pitolisant SPC states that treatment discontinuation should be monitored.

The SPC states that long-term efficacy data are limited and the continued efficacy of pitolisant should be regularly evaluated. In the published trials, pitolisant 5 mg to 40 mg per day was superior to placebo for improvements in excessive daytime sleepiness, time

awake in a darkened room and weekly cataplexy rate, but it was not established as non-inferior to modafinil 100 mg to 400 mg per day for improving excessive daytime sleepiness. In the unpublished pivotal trial pitolisant 5 mg to 20 mg per day was not superior to placebo for improving excessive daytime sleepiness.

In addition to effectiveness, safety and patient factors, local decision makers will need to take cost into account when considering the likely place in therapy of pitolisant. The 30-day cost of pitolisant at a dose of 4.5 mg to 36 mg once daily is £310.00 to £620.00 (MIMS, February 2017, excluding VAT). The 30-day cost of other medicines used for narcolepsy is £6.06 to £318.24 for stimulants such as modafinil, dexamfetamine or methylphenidate and £540.00 to £1,080.00 for sodium oxybate (Drug Tariff, February 2017, excluding VAT).

Information for the public about medicines

Evidence summaries provide an overview of the best evidence that is available about specific medicines. They also give general information about the condition that the medicine might be prescribed for, how the medicine is used, how it works, and what the aim of treatment is.

Evidence summaries aim to help healthcare professionals and patients decide whether medicines are safe to use and if they are likely to work well, especially when there isn't another suitable medicine that has a licence for the condition. They don't contain recommendations from NICE on whether the medicine should be used.

Information about licensing of medicines

In the UK, medicines need to have a licence before they can be widely used. To get a licence, the manufacturer of the medicine has to provide evidence that shows that the medicine works well enough and is safe enough to be used for a specific condition and for a specific group of patients, and that they can manufacture the medicine to the required quality. Evidence summaries explain whether a medicine has a licence, and if it does what the licence covers.

There is more information about licensing of medicines on NHS Choices.

Medicines can be prescribed if they don't have a licence (unlicensed) or for 'off-label' use. Off-label means that the person prescribing the medicine wants to use it in a different way than that stated in its licence. This could mean using the medicine for a different condition or a different group of patients, or it could mean a change in the dose or that the medicine is taken in a different way. If a healthcare professional wants to prescribe an unlicensed medicine, or a licensed medicine off-label, they must follow their professional guide, for example for doctors the General Medical Council's good practice guidelines. These include giving information about the treatment and discussing the possible benefits and harms so that the person has enough information to decide whether or not to have the treatment. This is called giving informed consent.

Questions that might be useful to ask about medicines

- Why am I being offered this medicine?
- Why am I being offered a medicine that is unlicensed or is being used off-label?
- What does the treatment involve?
- What are the benefits I might get?
- How good are my chances of getting those benefits?
- Could having the treatment make me feel worse?
- Are there other treatments I could try?
- What are the risks of the treatment?
- Are the risks minor or serious? How likely are they to happen?
- What could happen if I don't have the treatment?

Relevance to other NICE programmes

There is no NICE guidance on the treatment of narcolepsy.

This use of pitolisant is not appropriate for referral for a NICE technology appraisal and is not currently planned into any other work programme.

References

Baumann CR (2017) Wide implications of a trial on pitolisant for cataplexy. Lancet Neurology; published 24 January, DOI: http://dx.doi.org/10.1016/S1474-4422(16)30398-2

Billiard M, Bassetti C, Dauvilliers Y et al. (2006) EFNS guidelines on management of narcolepsy. European Journal of Neurology 13(10): 1035–48

Dauvilliers Y, Bassetti C, Lammers GJ et al. for the HARMONY I study group (2013) Pitolisant versus placebo or modafinil in patients with narcolepsy: a double-blind, randomised trial. Lancet Neurology 12(11): 1068–75

Sateia MJ (2014) International classification of sleep disorders-third edition: highlights and modifications. Chest 146(5): 1387–94

Szakacs Z, Dauvilliers Y, Mikhaylov V et al. for the HARMONY-CTP study group (2017) Safety and efficacy of pitolisant on cataplexy in patients with narcolepsy: a randomised, double-blind, placebo-controlled trial. Lancet Neurology; published 24 January, DOI: http://dx.doi.org/10.1016/S1474-4422(16)30333-7

Evidence tables

Table 4 Dauvilliers et al. 2013

Study reference	Dauvilliers Y, Bassetti C, Lammers GJ et al. for the HARMONY I study group (2013) Pitolisant versus placebo or modafinil in patients with narcolepsy: a double-blind, randomised trial. Lancet Neurology 12:1068–75
Unique identifier	NCT01067222
Study type	RCT
Aim of the study	To evaluate the efficacy and safety of pitolisant compared with placebo or modafinil in people with narcolepsy (with or without cataplexy)
Study dates	May 2009 to June 2010

Setting	32 centres in France, Germany, Netherlands, Hungary and Switzerland
Number of participants	n=95 randomised (94 in the ITT analysis[a])
Population	Adults aged 18 years or older with narcolepsy with or without cataplexy. Participants could not take psychostimulants for at least 14 days before baseline but could remain on sodium oxybate or non-tricyclic antidepressants at stable doses for treating cataplexy. Median age 33 to 40 years, 54% male, 81% had cataplexy, 45% had taken psychostimulants previously (mostly modafinil or methylphenidate), 35% were using sodium oxybate (n=8) or non-tricyclic antidepressants (n=25) throughout the trial. Mean baseline Epworth Sleepiness Scale (ESS) score was about 18.
Inclusion criteria	Participants had to meet the International Classification of Sleep Disorders-2 criteria for narcolepsy (with or without cataplexy); have self-reported excessive daytime sleepiness for more than 3 months; have narcolepsy confirmed by polysomogram, a multiple sleep latency test within the previous 5 years showing a mean sleep latency of 8 minutes or less with 2 or more sleep onset rapid eye movement periods, and an ESS score of 14 or more.
Exclusion criteria	Other disorder which could be the main cause of excessive daytime sleepiness in people without cataplexy (such as sleep apnoea), history of substance abuse, serious cardiovascular disorder, hepatic or renal abnormalities, psychiatric disorder. Use of tricyclic antidepressants. Women of child-bearing potential had to use effective contraception.
Intervention(s)	Pitolisant (n=32 randomised, n=31 in the ITT population) • 3 weeks of flexible dosing 10 mg, 20 mg or 40 mg per day[b] • 5 weeks of stable dosing

Comparator(s)	Modafinil (n=33) • 3 weeks of flexible dosing 100 mg, 200 mg or 400 mg per day[b] • 5 weeks of stable dosing Placebo (n=30)
Length of follow-up	8-week treatment phase plus 1-week withdrawal phase (all participants received placebo)
Outcomes	Primary outcome: • Difference in change in ESS score between pitolisant and placebo after 8 weeks (to demonstrate superiority)[c] • Difference in change in ESS score between pitolisant and modafinil after 8 weeks (to demonstrate non-inferiority[d] if superiority of pitolisant over placebo was demonstrated)
	Secondary outcomes: • Maintenance of wakefulness test (MWT) administered in 4 sessions • Sustained attention to response task (SART) administered in 4 sessions • Modified clinical global impression of change (CGI-C) targeting excessive daytime sleepiness and cataplexy • European quality of life questionnaire (EQ-5D) • Patients global opinion of their treatment • Symptoms of cataplexy assessed by patients' sleep diaries

	Safety outcomes: • Any adverse events • Haematology and blood chemistry tests, vital signs, electrocardiograms, and physical examination. • Occurrence of withdrawal syndrome (as defined in DSM-4) after treatment ended	
Source of funding	Bioprojet, France	
Overall risk of bias/quality assessment (CASP RCT checklist)	Did the trial address a clearly focused issue?	Yes
	Was the assignment of patients to treatments randomised?	Yes[e]
	Were patients, health workers and study personnel blinded?	Yes[f]
	Were the groups similar at the start of the trial?	Yes
	Aside from the experimental intervention, were the groups treated equally?	Yes
	Were all of the patients who entered the trial properly accounted for at its conclusion?	Yes
	How large was the treatment effect?	See table 1
	How precise was the estimate of the treatment effect?	See table 1
	Can the results be applied in your context? (or to the local population)	Unclear[g]
	Were all clinically important outcomes considered?	Yes
	Are the benefits worth the harms and costs?	See key points

Study limitations	• Small numbers of participants in the trial • Short duration of the trial • Flexible dosage and multiple visits could have affected efficacy • Limited generalisability to excluded populations and people not taking any other treatments for narcolepsy • People taking modafinil could have been aware of this because of its effects

Comments	[a] The intention to treat population included all participants who had at least 1 dose of study medication and at least 1 post-baseline assessment. One person withdrew consent after randomisation in the pitolisant group. [b] For the first 7 days all participants took a low dose (10 mg pitolisant, 100 mg modafinil or placebo). For the next 7 days all participants took a medium dose (20 mg pitolisant, 200 mg modafinil or placebo). At day 14, doses were adjusted based on individual clinical efficacy and safety assessed by investigators. Participants could take 10 mg, 20 mg or 40 mg of pitolisant; 100 mg, 200 mg or 400 mg modafinil; or placebo. At day 21 the dose could only be decreased for tolerance. Participants then continued on their assigned stable dose for 5 weeks. Treatment was stopped on day 56 and all participants received 1 week of placebo. Pitolisant was given once daily in the morning; modafinil was given twice daily in the morning and at lunchtime. (masked using double-dummy medication in sealed capsules). Pitolisant was given as pitolisant hydrochloride 10 mg, 20 mg or 40 mg which is equivalent to 9 mg, 18 mg or 36 mg of pitolisant. [c] Baseline ESS values were the mean of values at day −7 and day 0. Final ESS values were the mean of values at day 49 and day 56. Missing data were imputed using last observation carried forward. [d] If superiority of pitolisant over placebo was shown, non-inferiority of pitolisant versus modafinil could be tested based on a non-inferiority margin of 2 points on the ESS score. [e] The method of randomisation suggests allocation was concealed. Participants were randomised to each treatment group (1:1:1) via an interactive web response system with a computer generated randomisation sequence. The investigator at each site interacted confidentially with the system to communicate dosage strength allocation. [f] Treatment allocation was masked using double-dummy medication in sealed capsules. Double-blinding was maintained by all participants taking 4 capsules per day (2 before breakfast and 2 before lunch) whatever the treatment or dose. However, because of its effects, people taking modafinil may have become aware of their treatment allocation.

	[g] There is limited generalisability to excluded populations (children, severely ill people, those with unstable comorbidities, and those who declined to participate because they didn't want to receive placebo) and people who were not taking any other medicines for narcolepsy or cataplexy (35% continued sodium oxybate or non-tricyclic antidepressants).
Abbreviations: CGI-C, clinical global impression of change; DSM-4, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; EQ-5D, European quality of life questionnaire; ESS, Epworth Sleepiness Scale; ITT, intention to treat analysis; MWT, maintenance of wakefulness test; RCT, randomised controlled trial; SART, sustained attention to response task.	

Table 5Szakacs et al. 2017

Study reference	Szakacs Z, Dauvilliers Y, Mikhaylov V et al. for the HARMONY-CTP study group (2017) Safety and efficacy of pitolisant on cataplexy in patients with narcolepsy: a randomised, double-blind, placebo-controlled trial. Lancet Neurology; published 24 January, DOI: http://dx.doi.org/10.1016/S1474-4422(16)30333-7
Unique identifier	NCT01800045
Study type	RCT
Aim of the study	To evaluate the efficacy and safety of pitolisant on cataplexy compared with placebo in people with narcolepsy with cataplexy
Study dates	April 2013 to January 2015
Setting	16 centres in Bulgaria, Czech Republic, Hungary, Macedonia, Poland, Russia, Serbia, Turkey and Ukraine
Number of participants	n=106 randomised (105 in the ITT analysis[a])

Population	Adults aged 18 years or older with narcolepsy with cataplexy. Participants could not take psychostimulants or sedatives but could remain on sodium oxybate or antidepressants if doses were stable at least 1 month before randomisation and throughout the trial. Median age was 34 to 39 years and 50% were male. In the pitolisant group, the mean number of cataplexy episodes per week at baseline was 11, 41% of people had taken cataplexy medicines in the previous 3 months, and 7% continued these during the trial. In the placebo group, the mean number of cataplexy episodes per week at baseline was 9, 80% of people had taken cataplexy medicines in the previous 3 months, and 16% continued these during the trial. Mean baseline Epworth Sleepiness Scale (ESS) scores were about 17 in both groups.
Inclusion criteria	Participants had to meet the International Classification of Sleep Disorders-2 criteria for narcolepsy with cataplexy (defined as excessive daytime sleepiness and a history of cataplexy). This was confirmed in most people by polysomogram and a multiple sleep latency test within the previous year showing 2 or more sleep onset rapid eye movement periods, 3 or more cataplexies per week and an ESS score of 12 or more. There was a 3-week selection period before randomisation consisting of 1-week washout period and 2-week baseline period to collect baseline cataplexy data.
Exclusion criteria	Other disorder which could be the main cause of excessive daytime sleepiness (such as sleep apnoea), history of substance abuse, serious cardiovascular disorder, hepatic or renal abnormalities, psychiatric disorder. Women of child-bearing potential had to use effective contraception.
Intervention(s)	Pitolisant (n=54) • 3 weeks of flexible dosing 5 mg, 10 mg or 20 mg per day[b] • 4 weeks of stable dosing 5 mg, 10 mg, 20 mg or 40 mg per day
Comparator(s)	Placebo (n=52 randomised, n=51 in the ITT population)
Length of follow-up	7-week treatment phase plus 1-week withdrawal phase (all participants received placebo)

Outcomes	Primary outcome: • Change in the weekly cataplexy rate (average number of cataplexy attacks per week) between the 2 weeks of baseline and the 4 weeks of stable dosing[c]
	Secondary outcomes: • Weekly cataplexy rate changes in people maintained or not on anticataplectic medicines • Mean change in ESS score • Proportion of participants with a final ESS score of 10 or less • Proportion of participants with a weekly cataplexy rate above 15 (a non-validated cut-off) • Maintenance of wakefulness test (MWT) administered in 4 sessions • Modified clinical global impression of change (CGI-C) targeting excessive daytime sleepiness and cataplexy • European quality of life questionnaire (EQ-5D) • Patients global opinion of their treatment • Number of days with hallucinations (recorded in patients' diaries)
	Safety outcomes: • Any adverse events • Laboratory tests, vital signs, electrocardiograms, and physical examination. • Beck Depression Inventory • Occurrence of withdrawal syndrome (as defined in DSM-4) after treatment ended

Source of funding	Bioprojet, France	
Overall risk of bias/quality assessment (CASP RCT checklist)	Did the trial address a clearly focused issue?	Yes
	Was the assignment of patients to treatments randomised?	Yes[d]
	Were patients, health workers and study personnel blinded?	Yes[e]
	Were the groups similar at the start of the trial?	Unclear[f]
	Aside from the experimental intervention, were the groups treated equally?	Yes
	Were all of the patients who entered the trial properly accounted for at its conclusion?	Yes
	How large was the treatment effect?	See table 1
	How precise was the estimate of the treatment effect?	See table 1
	Can the results be applied in your context (or to the local population)?	Unclear[g]
	Were all clinically important outcomes considered?	Yes
	Are the benefits worth the harms and costs?	See Key points

Study limitations	• Small numbers of participants in the trial • Short duration of the trial • Flexible dosage and multiple visits could have affected efficacy • Limited generalisability to excluded populations • Conducted mainly in Eastern European countries, which may not reflect UK clinical practice • High placebo effect on weekly cataplexy rate • Baseline differences between groups in the mean number of cataplexy episodes per week and proportion of people who had previously taken or were continuing to take cataplexy medicines

Comments	[a] The intention to treat population included all participants who had at least 1 dose of study medication. One person did not receive treatment in the placebo group. [b] For the first 7 days all participants took 5 mg pitolisant or placebo. For the next 7 days all participants took 10 mg pitolisant or placebo. At day 14, doses were adjusted based on individual clinical efficacy and safety assessed by investigators. Participants could take 5 mg, 10mg or 20 mg of pitolisant; or placebo. At day 21 the dose could be adjusted again to the final dose of 5 mg, 10 mg, 20 mg or 40 mg. Participants then continued on their assigned stable dose for 4 weeks. Treatment was then stopped and all participants received 1 week of placebo. Pitolisant was given once daily in the morning, as pitolisant hydrochloride 5 mg, 10 mg, 20 mg or 40 mg (which is equivalent to 4.5 mg, 9 mg, 18 mg or 36 mg of pitolisant). [c] Participants reported in diaries all cataplexy attacks defined as sudden and transient partial or generalised loss of muscle tone triggered by emotion. [d] The method of randomisation suggests allocation was concealed. Participants were randomised to each treatment group (1:1) via an interactive web response system with a computer generated randomisation sequence. [e] Treatment allocation was masked to both patients and investigators using medication in sealed capsules. However, because of its effects, people taking pitolisant may have become aware of their treatment allocation. [f] There were baseline differences between the pitolisant and placebo group in the mean number of cataplexy episodes per week (11 in the pitolisant group; 9 in the placebo group) and proportion of people who had taken cataplexy medicines in the previous 3 months (41% in the pitolisant group at baseline with 7% continuing during the trial; 80% in the placebo group at baseline with 16% continuing during the trial). [g] There is limited generalisability to excluded populations (children, those with unstable comorbidities, and those who declined to participate because they didn't want to receive placebo).

Abbreviations: CGI-C, clinical global impression of change; DSM-4, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; EQ-5D, European quality of life questionnaire; ESS, Epworth Sleepiness Scale; ITT, intention to treat analysis; MWT, maintenance of wakefulness test; RCT, randomised controlled trial.

Results tables

Table 6 Dauvilliers et al. 2013

	Pitolisant	Modafinil	Placebo	Analysis
n (ITT)[a]	**31**	**33**	**30**	
Primary outcome				
Mean change from baseline in ESS score after 8 weeks	−5.8 from baseline of 17.8	−6.9 from baseline of 18.5	−3.4 from baseline of 18.9	Pitolisant versus placebo (superiority test); mean difference: −3.0 (95% CI −5.6 to −0.4), p=0.024 Pitolisant versus modafinil (non-inferiority test); mean difference: 0.12 (95% CI −2.5 to 2.7), p=0.250, NS[b]
Selected secondary outcomes				
MWT (minutes)	Baseline: 7.4 Final: 9.7 Change[c]: 1.32	Baseline: 8.8 Final: 15.1 Change[c]: 1.72	Baseline: 8.4 Final: 7.6 Change[c]: 0.88	Pitolisant versus placebo; ratio: 1.47 (95% CI 1.01 to 2.14), p=0.044 Pitolisant versus modafinil; ratio: 0.77 (95% CI 0.52 to 1.13), p=0.173, NS

SART-total score	Baseline: 12.5 Final: 10.0 Change[c]: 0.8	Baseline: 11.6 Final: 10.4 Change[c]: 0.89	Baseline: 11.5 Final: 11.4 Change[c]: 1.0	Pitolisant versus placebo; ratio: 0.80 (95% CI 0.64 to 1.00), p=0.053, NS Pitolisant versus modafinil; ratio: 0.90 (95% CI 0.71 to 1.14), p=0.370, NS
Safety and tolerability outcomes				
n	**31**	**33**	**30**	
Participants with adverse events	71% (22/31)	79% (26/33)	33% (10/30)	No analysis reported
Participants with serious adverse events	3% (1/31)	15% (5/33)	0	No analysis reported

Abbreviations: CI, confidence interval; ESS, Epworth Sleepiness Scale; ITT, intention to treat analysis; MWT, maintenance of wakefulness test; n, number of participants; NS, not significant; p, p value; SART, sustained attention to Response task.

[a] The intention to treat population included all participants who had at least 1 dose of study medication and at least 1 post-baseline assessment. One person withdrew consent after randomisation in the pitolisant group.

[b] Non-inferiority was not shown based on the pre-specified non-inferiority margin of 2 points.

[c] Change calculated as final/baseline.

Table 7 Szakacs et al. 2017

	Pitolisant	Placebo	Analysis
n (ITT)[a]	**54**	**51**	
Primary outcome			

Mean change in average number of cataplexy attacks per week after 7 weeks (weekly cataplexy rate)	Baseline: 9.15 Final: 2.27 Change[b]: 0.25	Baseline: 7.31 Final: 4.52 Change[b]: 0.62	Pitolisant versus placebo; rate ratio: 0.51 (95% CI 0.44 to 0.60), p<0.0001
Selected secondary outcomes			
Mean change from baseline in ESS score after 7 weeks	−5.4 from baseline of 17.4	−1.9 from baseline of 17.3	Pitolisant versus placebo; mean difference: −3.48 (95% CI −5.03 to −1.92), p=0.0001
MWT (minutes)	Baseline: 3.54 Final: 6.91 Change[b]: 1.95	Baseline: 4.08 Final: 4.32 Change[b]: 1.06	Pitolisant versus placebo; ratio: 1.85 (95% CI 1.24 to 2.74), p=0.003
Safety and tolerability outcomes			
n	**54**	**51**	
Participants with adverse events	35% (19/54)	31% (16/51)	p=0.528
Participants with severe adverse events	2% (1/54)	0	No analysis reported

Abbreviations: CI, confidence interval; ESS, Epworth Sleepiness Scale; ITT, intention to treat analysis; MWT, maintenance of wakefulness test; n, number of participants; p, p value.

[a] The intention to treat population included all participants who had at least 1 dose of study medication and at least 1 post-baseline assessment. One person did not receive treatment in the placebo group.

[b] Change calculated as final/baseline.

Excluded studies

Study reference	Reason for exclusion
Dauvilliers Y (2014) Novel therapeutic approach in narcolepsy: Clinical trials of an antagonist/inverse agonist of the histamine H3 receptor. Journal of sleep research 23: 75 (282)	Abstract only Duplicate of included study (HARMONY 1)
Leu-Semenescu S, Nittur N, Golmard JL et al. (2014) Effects of pitolisant, a histamine H3 inverse agonist, in drug-resistant idiopathic and symptomatic hypersomnia: a chart review. Sleep Medicine 15: 681–7	Poor relevance against search terms Not licensed indication

The European Public Assessment Report (EPAR) for pitolisant states that the narcolepsy development programme included 5 phase III trials, of which HARMONY I and HARMONY Ibis were considered pivotal for the indication in the treatment of narcolepsy with or without cataplexy.

- HARMONY I (NCT01067222) has been completed and published in full (Dauvilliers et al. 2013).
- HARMONY Ibis (NCT01638403) has been completed but has not been published.
- HARMONY III (NCT01399606) was due to complete in October 2016.
- HARMONY IV (NCT01789398) has been completed but has not been published.
- HARMONY CTP (NCT01800045) has been completed and published in full (Szakacs et al. 2017).

Terms used in this evidence summary

Epworth Sleepiness Scale

The Epworth Sleepiness Scale (ESS) is a self-administered patient questionnaire with 8 questions asking how likely people are to doze off or fall asleep in 8 life situations, such as watching television. Each question is ranked 0=would never doze, 1=slight chance of dozing, 2=moderate chance of dozing, 3=high chance of dozing. The maximum score is 24, with higher scores indicating more chance of dozing off (Johns 1991). The minimum clinically important difference on this scale is 3 points (Dauvilliers 2013, European Public Assessment Report [EPAR] for pitolisant).

Maintenance of wakefulness test

The maintenance of wakefulness test (MWT) measures the ability of people to stay awake for a defined period of time. It consists of 4×40-minute trials performed at 2-hour intervals, with the first trial beginning about 1.5 to 3 hours after the person's usual wake-up time. The person is seated in bed in an otherwise dark room with a light source positioned slightly behind their head. The ability to stay awake is measured in minutes. Sleep onset is defined as the first epoch of greater than 15 seconds of cumulative sleep in a 30-second epoch. Trials are ended after 40 minutes if no sleep occurs, or after unequivocal sleep, defined as 3 consecutive epochs of stage 1 sleep, or 1 epoch of any other stage of sleep. Among normal control subjects, mean sleep latency to first epoch of sleep is about 30 minutes (Littner at al. 2005, van der Heide et al. 2015).

Sustained attention to response test

The sustained attention to response test (SART) is a computer-based task designed to measure a person's ability to withhold responses to infrequent and unpredictable stimuli during a period of rapid and rhythmic responding to frequent stimuli. For example, people are presented with the digits 1 to 9 in random order and they are asked to respond as quickly as possible by clicking the mouse, apart from when they see the number 3 when they must withhold the response. The task consists of a total of 225 trials (25 of each of the 9 digits) and lasts approximately 4 minutes. SART comprises of 3 error scores: the number of times the button was pressed inappropriately ('NO GO'; with a maximum count of 25), the number of times key pressing was missed ('GO'; with a maximum count of 200), and the sum of these 2 scores (Fronczek et al. 2006, Dauvilliers 2013, van der Heide et al. 2015). Lower scores indicating better attention levels.

Search strategy

Database: Medline, Version: Ovid MEDLINE(R) without Revisions <1996 to October Week 3

2016

Search date: 31 Oct 2016

1 pitolisant/ (0)

2 (wakix or pitolisant or tiprolisant).mp. (25)

3 ("BF2.649" or BF2649).tw. (14)

4 1 or 2 or 3 (31)

5 randomized controlled trial.pt. (326071)

6 randomized controlled trial/ (326071)

7 controlled clinical trial.pt. (45571)

8 random allocation/ (53154)

9 Placebos/ (15215)

10 clinical trial, phase ii/ or clinical trial, phase iii/ (34048)

11 5 or 6 or 7 or 8 or 9 or 10 (445020)

12 animals/ (3182882)

13 humans/ (9075526)

14 12 not 13 (2049165)

15 11 not 14 (395896)

16 4 and 15 (4)

Database: Medline in-process, Version: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present

Search date: 31 Oct 2016

1 (wakix or pitolisant or tiprolisant).mp. (41)

2 ("BF2.649" or BF2649).tw. (16)

3 1 or 2 (47)

4 narcoleps*.mp. or sleep*.tw. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (139373)

5 3 and 4 (25)

6 3 not 5 (22)

Database: Embase, Version: Ovid Embase <1996 to 2016 October 28>

Search date: 31 Oct 16

1 pitolisant/ (121)

2 (wakix or pitolisant or tiprolisant).mp. (136)

3 ("BF2.649" or BF2649).tw. (22)

4 1 or 2 or 3 (140)

5 *randomized controlled trial/ (37393)

6 *Randomization/ (1552)

7 *Placebo/ (24243)

8 *Crossover Procedure/ (3691)

9 (random or randomi* or randoml*).tw. (1007657)

10 rct*.tw. (43260)

11 (phase 4 or phase iv or phase 3 or phase iii).tw. (63910)

12 placebo*.tw. (197827)

13 (crossover* or (cross adj over*)).tw. (64591)

14 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 (1128664)

15 Nonhuman/ (3576468)

16 Human/ (12824354)

17 15 not (15 and 16) (2416322)

18 14 not 17 (1041943)

19 4 and 18 (24)

20 limit 19 to conference abstract (7)

21 19 not 20 (17)

Databases: Cochrane/CRD databases, Version: Wiley

Search date: 31 Oct 16

1 wakix or pitolisant or tiprolisant:ti,ab,kw (Word variations have been searched) 8

#2 "BF2.649" or BF2649:ti,ab,kw 4

#3 #1 or #2 8

Development of this evidence summary

The evidence summary: process guide (2017) sets out the process NICE uses to select topics for evidence summaries and details how the summaries are developed, quality

assured and approved for publication.

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Declarations of interest

Dr Paul Reading: Speaker fees for educational meetings on various sleep topics from UCB Pharma and AstraZeneca.

Dr Zenobia Zaiwalla: No interests declared. Leads on the non-respiratory paediatric and adult sleep disorder service at the John Radcliffe Hospital.

Prof Adam Zeman: No interests declared.

About this evidence summary

Evidence summaries provide a summary of the best available published evidence for selected new medicines, unlicensed medicines or off-label use of licensed medicines.

The summaries assess the strengths and weaknesses of the best available evidence to inform health professionals and commissioners' decision-making.

This summary is not NICE guidance.

ISBN: 978-1-4731-2380-9