New Medicine Recommendation
Pitolisant 4.5mg/18mg tablets (Wakix®)
For Treatment of Narcolepsy with or without Cataplexy in adults

Recommendation:

Black

Pitolisant tablets are not recommended for use across the Lancashire NHS health economy for the treatment of narcolepsy with or without cataplexy. Pitolisant did not demonstrate non-inferiority compared to modafinil and is significantly more expensive than other treatments available in Lancashire for the management of narcolepsy with or without cataplexy.

Summary of supporting evidence:

- In the Harmony I study, the primary analysis of between-group differences in mean Epworth Sleepiness Scale (ESS) score at endpoint (adjusted for baseline) showed pitolisant to be superior to placebo (difference –3·0, [CI95% –5·6; –0·4, p=0·024]).
- The non-inferiority of pitolisant compared to modafinil was not demonstrated in both the Harmony I and Harmony Ibis Studies.
- In the Harmony CTP study, pitolisant produced significant improvements in the weekly cataplexy rate (WCR), decreasing from 7.31 to 6.79 for placebo and 9.15 to 3.28 for pitolisant, with a ratio rate (Pitolisant/Placebo) = 0.512 [CI95% 0.435; 0.603, p<0.0001]).
- The EMEA stated that, based on available data, the safety profile of pitolisant in the treatment of narcolepsy with or without cataplexy is acceptable. However, the EMEA also noted that the long-term safety database for pitolisant in narcolepsy patients is limited.
- Treatment should be initiated, evaluated and discontinued in secondary care by a clinician experienced in the treatment of sleep disorders.
- There are limited safe and well tolerated treatment options for the management of narcolepsy with cataplexy.
## Details of Review

| **Name of medicine** (generic & brand name): | Pitolisant tablets (Wakix®) |
| **Strength(s) and form(s):** | Oral tablets 4.5mg/18mg |

### Dose and administration:

Wakix should be used at the lowest effective dose, depending on individual patient response and tolerance, according to an up-titration scheme, without exceeding the dose of 36 mg/day:

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

At any time the dose can be decreased (down to 4.5 mg per day) or increased (up to 36 mg per day) according to the physician assessment and the patient’s response. The total daily dose should be administered as a single dose in the morning during breakfast. [1]

### BNF therapeutic class / mode of action

Narcolepsy / Histamine H3 receptor inverse agonist.

### Licensed indication(s):

Treatment of narcolepsy with or without cataplexy in adult patients.

### Proposed use (if different from, or in addition to, licensed indication above):

### Course and cost:

4.5mg x 30 tablets = £310; 18mg x 30 tablets = £310

Annual cost range: £3,834 - £14,570 (price based on patient requiring maintenance dose of 4.5mg or 18mg [one daily] compared to dose of 31.5mg [four daily]. [2]

### Current standard of care/comparator therapies:

Modafinil is licensed for excessive sleepiness associated with narcolepsy with or without cataplexy. Clomipramine is licensed for adjunctive treatment of cataplexy associated with narcolepsy. Dexamfetamine and methylphenidate (unlicensed indication) are listed in the Lancashire Care Foundation Trust Joint Formulary for Psychotropic Medication for the treatment of narcolepsy [3].

The European Academy of Neurology guidelines for the management of narcolepsy in adults [4] recommend the following for excessive daytime sleepiness and irresistible episodes of sleep:

- In cases when the most disturbing symptom is excessive daytime sleepiness, modafinil should be prescribed based on its efficacy, limited adverse effects, and ease of manipulation.
- When excessive daytime somnolence coexists with cataplexy and poor sleep, sodium oxybate may be prescribed; vigilance should be held for the possible development of sleep - disordered breathing; depressed patients should not be treated with this drug.
- Supplementation with modafinil is generally more successful than sodium oxybate alone.
- **Methylphenidate** may be an option in case modafinil is insufficiently active and sodium oxybate is not recommended.

**Cataplexy:**

- First line - pharmacological treatment of cataplexy is **sodium oxybate**. The drug should not be used in association with other sedatives, respiratory depressants, and muscle relaxants. Vigilance should be held for the possible development of sleep - disordered breathing, and depressed patients should not be treated with the drug.
- Second line – **tricyclic antidepressants**, particularly **clomipramine** (10 – 75 mg), are potent anticataplectic drugs.
- **SSRIs** are slightly less active but have fewer adverse effects.
- The noradrenaline-serotonin reuptake inhibitor **venlafaxine** is widely used today but lacks any published clinical evidence of efficacy.
- The noradrenaline reuptake inhibitors, such as **reboxetine** and **atomoxetine**, also lack published clinical evidence.

**Relevant NICE guidance:**

None
Background and context

Narcolepsy is a debilitating lifelong rapid eye movement (REM) sleep disorder. The main symptoms of this condition include: excessive daytime sleepiness (EDS) with irresistible sleep attacks, cataplexy (sudden bilateral loss of muscle tone), hypnagogic hallucinations and sleep paralysis. Other symptoms can include loss of concentration and memory. The two main groups of patients with narcolepsy are patients suffering narcolepsy with cataplexy and patients who do not suffer cataplexy. [3]

Narcolepsy is diagnosed according to the international classification of sleep disorders (ICSD-3). Diagnostic methods include a combination of history taking, polysomnography and multiple sleep latency tests alongside the measurement of hypocretin levels in cerebrospinal fluid. [3]

Conventional treatments aim to control symptoms and are not curative. Modafinil is used first line for the treatment of excessive sleepiness associated with narcolepsy with or without cataplexy. Dexamphetamine and methylphenidate (unlicensed) can also be used to treat narcolepsy. [5] None of these treatments reduce the frequency of cataplexy attacks. Antidepressants are often prescribed for patients with narcolepsy with cataplexy as an adjunct. For example, clomipramine is licensed as an adjunctive treatment of cataplexy associated with narcolepsy. [5]

Modafinil is a wake-promoting drug similar in structure to amphetamine [3] that is effective in the treatment of excessive daytime sleepiness, but not cataplexy. [6] A Cochrane review in 2010 found that there was insufficient evidence to support antidepressants for the treatment of cataplexy despite being widely used for this purpose (European guidelines support their use). [7] [8] The evidence supporting the use of existing combination therapy, e.g. modafinil and clomipramine, is mixed.

Sodium oxybate was licensed in the European Union in 2007 for the ‘treatment of narcolepsy with cataplexy in adult patients’. [9] Sodium oxybate has been approved for the treatment of cataplexy associated with narcolepsy in the US since 2002. However, a condition of approval was the implementation of a risk management programme (RMP). The RMP was implemented to mitigate the risks associated with the use of sodium oxybate both historically as a drug of abuse or potential co-administration with alcohol and any other CNS depressants. [10] Sodium oxybate is currently not recommended as a treatment for narcolepsy with cataplexy in Lancashire. The LMMG assigned sodium oxybate a “black” RAG status following a New Medicine Review which raised significant concerns regarding the safety and cost effectiveness of sodium oxybate.

Pitolisant is an orally active antagonist/inverse agonist of the human histamine H3 receptor. It works by enhancing histaminergic transmissions in brain, acetylcholine release in prefrontal cortex and hippocampus and dopamine release in the prefrontal cortex but not in the striatum. Histaminergic neurons are mainly located in the posterior hypothalamus. They play a role in arousal mechanisms. It has been shown that histamine H3 receptors (H3R), only activated by inverse agonists, were able to promote activation of cerebral histamine neurons. [11]
Summary of evidence
Summary of efficacy data in proposed use:

### Pivotal Studies

Data from two pivotal double-blind, randomised, parallel-group controlled studies were submitted to the EMEA in support of pitolisant’s indication “for the treatment of narcolepsy with or without cataplexy”. [1] The studies were the Harmony I study (n=110) [12] and the Harmony Ibis study (n=183). [11]

Both studies recruited patients with narcolepsy from multiple European sites. Patients were eligible for inclusion if they were aged 18 years or older, had not taken psychostimulants for at least 14 days, and had excessive daytime sleepiness (EDS) as defined by an Epworth Sleepiness Scale (ESS) score of at least 14. The ESS is based on the risk of dozing in eight common situations, scoring between 0 and 24 where 24 is the highest risk of dozing. [13] A computer-generated randomisation sequence randomly allocated patients to receive pitolisant, modafinil, or placebo (1:1:1). Treatment lasted 8 weeks: 3 weeks of flexible dosing according to investigator’s judgment followed by 5 weeks of stable dosing. Patients took either placebo, pitolisant or modafinil tablets sealed within capsules in a double-dummy design to ensure masking. The primary analysis assessed the superiority of pitolisant versus placebo, and the non-inferiority of pitolisant versus modafinil for the mean change from baseline in the ESS score. [11]

#### Harmony I

In the Harmony I study, mean ESS score reductions from baseline were -3.6 (SD± 5.6) in the placebo group, -4.6 (SD± 4.6) in the pitolisant 20mg/day group and -7.8 (SD± 5.9) in the modafinil group. The objective of the primary efficacy analysis was to demonstrate the superiority of pitolisant to placebo but the result was below the minimum clinically relevant difference of 3 points (difference= -1.88; [CI95% -5.26; 1.49]). The second analysis of non-inferiority of pitolisant compared to modafinil with a predefined non-inferiority margin threshold of 2 points was performed, leading to rejection of non-inferiority of pitolisant compared to modafinil (difference= -2.75; [CI95% -4.48; -1.02]). Furthermore, when superiority testing comparing pitolisant to modafinil was performed (sensitivity analysis), modafinil showed significantly (p<0.002) better results on ESS Final score (difference= -2.75 points). [11]

#### Harmony Ibis

In the Harmony Ibis study, mean ESS score reductions from baseline were -3.6 (SD± 5.6) in the placebo group, -4.6 (SD± 4.6) in the pitolisant 20mg/day group and -7.8 (SD± 5.9) in the modafinil group. The objective of the primary efficacy analysis was to demonstrate the superiority of pitolisant to placebo but the result was below the minimum clinically relevant difference of 3 points (difference= -1.94; [CI95% -4.05; 0.07]). The second analysis of non-inferiority of pitolisant compared to modafinil with a predefined non-inferiority margin threshold of 2 points was performed, leading to rejection of non-inferiority of pitolisant compared to modafinil (difference= -2.75; [CI95% -4.48; -1.02]). Furthermore, when superiority testing comparing pitolisant to modafinil was performed (sensitivity analysis), modafinil showed significantly (p<0.002) better results on ESS Final score (difference= -2.75 points). [11]

### Other efficacy data:

#### Harmony III

This was a 12 month phase III, open-label, prospective, longitudinal, study to assess the long-term safety of pitolisant in the treatment of Excessive Daytime Sleepiness (EDS) in narcolepsy (prolonged follow-up). This study enrolled patients who completed a double blind controlled study with pitolisant (The Harmony trials) or patients who in the opinion of the investigator would not have been able to participate in a double-blind study but could benefit from pitolisant (5,10,20 or 40mg daily). In this study, 102 narcoleptic patients with or without cataplexy were included, aged 18 to 69 years old, with a required baseline ESS score at inclusion ≥12 (mild to severe form of...
disease). The main results showed that the ESS change from baseline to final visit was about -4.3 points, overall of the same magnitude of what was observed in Harmony I (-5.8 points) and Harmony Ibis (-4.6 points). [11]

**Harmony CTP [14]**

For this randomised, double-blind, placebo-controlled trial, 117 patients experiencing at least three cataplexies per week were recruited then randomly assigned to receive either pitolisant or placebo once per day (1:1 ratio). Patients were eligible if they were aged 18 years or older and diagnosed with narcolepsy with cataplexy according to version two of the International Classification of Sleep Disorders criteria, [15] and had excessive daytime sleepiness (defined as an Epworth Sleepiness Scale score ≥12). Treatment lasted for 7 weeks: 3 weeks of flexible dosing decided by investigators according to efficacy and tolerance (5 mg, 10 mg, or 20 mg oral pitolisant), followed by 4 weeks of stable dosing (5 mg, 10 mg, 20 mg, or 40 mg). The primary endpoint was the change in the average number of cataplexy attacks per week as recorded in patient diaries (weekly cataplexy rate [WCR]) between the 2 weeks of baseline and the 4 weeks of stable dosing period.

The primary analysis showed a significant improvement in the pitolisant group at end of the stable dose treatment period. The WCR had decreased from 7.31 and 9.15 for placebo and pitolisant respectively to 6.79 and 3.28 for placebo and pitolisant respectively, with a ratio rate (Pitolisant/Placebo) =0.512 (CI95% 0.435; 0.603, p<0.0001). The results from this supportive study also showed a superior efficacy of pitolisant compared to placebo on EDS symptoms assessed with the ESS scores (observed mean changes were -1.9 ± 4.3 and -5.4 ± 4.3 for placebo and pitolisant groups, respectively). The difference was statistically significant (p<0.001) and clinically relevant.
Summary of Safety Data:

The clinical development program for pitolisant included a total of 1837 subjects. Of these, 1385 patients were exposed to pitolisant (291 healthy volunteers, 1094 patients including 342 patients in the treatment of narcolepsy and 752 in other indications). Data on long-term exposure (up to 12 months) in narcoleptic patients was available from the non-pivotal study Harmony III. 104 patients were included and 102 took at least one dose of study treatment. 68 patients completed the first 12-month treatment period and 34 withdrew from the study prematurely.

From pooled data of all the studies, the most frequently observed adverse events with pitolisant were headache (11.4%) and insomnia (9.0%). The EMEA identified similar trends in the data from narcolepsy studies, although the percentage of patients who reported weight increase (2.9%), anxiety (3.5%), vomiting (2.3%), diarrhoea (2.0%) and irritability (3.2%) were slightly more pronounced than when considering pooled data from all indications. Psychiatric disorders (21.9%) were reported more frequently with pitolisant, compared to placebo (8.9%) and modafinil (13.3%). Gastro-intestinal disorders were also more frequently reported with pitolisant (16.1%) than with placebo (8.2%). Inversely, nervous system disorders were slightly less reported with pitolisant (22.8% vs 23.5% modafinil vs 20.9% placebo). The frequency of reported adverse events increased with increasing doses of pitolisant in the pooled narcolepsy studies.

In the narcolepsy studies, 17 serious AEs were reported by 13 patients. All were considered by investigators as unrelated to studied treatment except for a case of miscarriage where causality was noted as possible. No deaths were reported.

The SPC for pitolisant (Wakix®) lists the following adverse effects: [1]

<table>
<thead>
<tr>
<th>Incidence of event</th>
<th>Adverse event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common (≥1/10)</td>
<td>None listed</td>
</tr>
<tr>
<td>Common (≥1/100 to &lt;1/10)</td>
<td>Insomnia, anxiety, irritability, depression, sleep disorder, vertigo, fatigue, headache, dizziness, tremor, nausea, vomiting, dyspepsia</td>
</tr>
<tr>
<td>Uncommon (≥1/1000 to &lt;1/100)</td>
<td>Agitation, hallucination (visual, auditory), affect lability, abnormal dreams, dysomnia, middle insomnia, initial insomnia, terminal insomnia, nervousness, tension, apathy, nightmare, restlessness, panic attack, libido changes, appetite changes, fluid retention, dyskinesia, balance disorder, cataplexy, disturbance in attention, dystonia, on and off phenomenon, hypersomnia, migraine, psychomotor hyperactivity, restless legs syndrome, somnolence, epilepsy, bradykinesia, paresthesia, visual acuity reduced, blepharospasm, tinnitus, extrasystoles, bradycardia, hyper/hypotension, hot flush, yawning, dry mouth, abdominal pain/discomfort, diarrhoea, constipation, gastroesophageal reflux disease, gastritis, gastrointestinal pain, hyperacidity, paraesthesia oral, erythema, pruritus, rash, hyperhidrosis, pollakiuria, metorrhagia, asthenia, chest pain, feeling abnormal, malaise oedema, peripheral oedema, weight changes, hepatic enzymes increased, electrocardiogram QT prolonged, heart rate increased, gamma-glutamyltransferase increased</td>
</tr>
<tr>
<td>Rare (≥1/10,000 to &lt;1/1000)</td>
<td>Anorexia, hyperphagia, appetite disorder, abnormal behaviour, confusional state, depressed mood, excitability, excitability, obsessive thoughts, dysphoria, hypnopompic/hypnagogic hallucination, mental impairment, loss of consciousness, tension headache, memory impairment, poor sleep quality, abdominal distension, dysphagia, flatulence, odynophagia, enterocolitis, toxic skin eruption, photosensitivity, neck pain, musculoskeletal chest pain, abortion spontaneous, pain, night sweats, sense of oppression, creatine phosphokinase increased, general physical abnormal, electrocardiogram repolarisation abnormality/ T wave inversion</td>
</tr>
</tbody>
</table>

The use of pitolisant is contraindicated in patients with severe hepatic impairment, hypersensitivity to the active substance/ excipients and in breastfeeding.

Pitolisant should be administered with caution in patients with acid related gastric disorders (including concomitant use of NSAIDs), obesity or severe anorexia. Caution should be taken when using pitolisant with epilepsy, severe depression or severe anxiety. In clinical trials, no specific cardiac safety signal was identified at therapeutic doses of pitolisant. Nevertheless, patients with
cardiac disease, co-medicating with other QT-prolonging medicinal products or medicines known to increase the risk of repolarization disorders, or patients at risk of increased exposure to pitolisant should be carefully monitored. Women of childbearing potential have to use effective contraception during treatment and at least up to 21 days after treatment discontinuation.

Co-administration of pitolisant with potent CYP3A4 inducers (e.g. rifampicin, phenobarbital, carbamazepine, phenytoin) or CYP2D6 inhibitors (e.g. paroxetine, fluoxetine, venlafaxine, duloxetine, bupropion, quinidine, terbinafine, cinacalcet) should be done with caution and dosage adjustments may be necessary. The combination of pitolisant with substrates of CYP3A4 and having a narrow therapeutic margin should be avoided. Pitolisant may reduce the effectiveness of hormonal contraceptives. Therefore, an alternative method of effective contraception should be used if the woman patient is using hormonal contraceptives. Tri or tetracyclic antidepressants (e.g. imipramine, clomipramine, mirtazapine) and sedating anti-histamines (e.g. pheniramine maleate, chlorpheniramine, diphenhydramine, promethazine, mepyramine) may impair the efficacy of pitolisant. Caution is advised when pitolisant is administered with a substrate of OCT1 (e.g. metformin). [1]

The EMA deemed that the safety profile of pitolisant is consistent with its mechanism of action and is considered acceptable in the treatment of narcolepsy with or without cataplexy. No major safety concern was identified in the clinical trials and the EMA concluded that adverse events can often be managed by individual dose adaptation. [11]

Strengths and limitations of the evidence:

Strengths

- Pitolisant has demonstrated a statistically significant effect, reduction in the Epworth Sleepiness Scale (ESS) in the Harmony I placebo controlled trial.
- The Harmony CTP study showed a significant improvement in the weekly cataplexy rate compared to placebo and further supported the effect of pitolisant in reducing the ESS score.
- The EMEA stated that based on available data, the safety profile of pitolisant is acceptable in the treatment of narcolepsy with or without cataplexy.
- Other treatment options licensed for narcolepsy and cataplexy (sodium oxybate, modafinil and clomipramine) have limitations with their tolerability and safety profiles.

Weaknesses

- The pivotal trials had a short duration and were only conducted in a small number of patients.
- Non-inferiority of pitolisant with modafinil was not proved in the pivotal studies and for the primary endpoint in Harmony Ibis pitolisant was not shown to be statistically superior to placebo.
- One of the pivotal studies (Harmony Ibis) was underpowered leading to inconsistencies in the ESS results.
- The safety data has been accrued from several studies investigating pitolisant’s use for indications other than narcolepsy. The safety database for pitolisant in narcolepsy patients is limited.
- The potential for “drug abuse and misuse” and “drug dependence” could not be excluded due to the lack of long-term data; abuse potential and risk of dependence have been included in the drug’s Risk Management Plan as important potential risk.

Summary of evidence on cost effectiveness:

No cost effectiveness data has been published.
Prescribing and risk management issues:

Treatment should be initiated by a clinician experienced in the treatment of sleep disorders. As long-term efficacy data are limited, the continued efficacy of treatment should be regularly evaluated by the clinician. No rebound effect was reported during clinical trials; however, treatment discontinuation should be monitored. Pitolisant is a 'black triangle' medicine - the Commission on Human Medicines (CHM) and the MHRA encourages the reporting of all suspected adverse reactions (side effects) to newer drugs and vaccines, which are denoted by the Black Triangle symbol. [16]

Commissioning considerations:

Comparative unit costs:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Example regimen</th>
<th>Cost per patient per course/ per year (ex VAT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pitolisant tablets</td>
<td>4.5mg-36mg daily</td>
<td>£3,834- £14,570 (typically £7,543 based on 36mg daily) Price range based on patient requiring maintenance dose of 18mg [one tablet daily] compared to dose of 31.5mg [four tablets daily].</td>
</tr>
<tr>
<td>Sodium oxybate oral solution</td>
<td>2.25g - 9g daily</td>
<td>£3,276- £13,104</td>
</tr>
<tr>
<td>Clomipramine capsules</td>
<td>10mg - 75mg daily</td>
<td>£18 -£46</td>
</tr>
<tr>
<td>Modafinil tablets</td>
<td>200-400mg daily</td>
<td>£158- £389</td>
</tr>
<tr>
<td>Dexamfetamine tablets</td>
<td>10-60mg daily</td>
<td>£644- £3,861</td>
</tr>
<tr>
<td>Methylphenidate tablets</td>
<td>10-60mg daily [8]</td>
<td>£67- £407</td>
</tr>
</tbody>
</table>

Associated additional costs or available discounts:

None

Productivity, service delivery, implementation:

Treatment should be initiated and continued in secondary care by a clinician experienced in the treatment of sleep disorders.

Anticipated patient numbers and net budget impact:

Narcolepsy with cataplexy is a rare and disabling disorder estimated to affect between 25 and 50 per 100,000 population. [11] Based on this assumption there are 375-750 patients with the condition in Lancashire. According to the European Handbook of Neurological Management guidelines, modafinil is the first line treatment for narcolepsy while sodium oxybate is suggested as the first line treatment in narcolepsy where cataplexy exists. [4] Sodium oxybate is not recommended for prescribing in Lancashire therefore clomipramine, the second line treatment option has been included for comparison in the table below.

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1 The manufacturer of pitolisant estimates that 66% of patients will be treated with the 36mg dose.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Total items</th>
<th>Total cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modafinil</td>
<td>2,926</td>
<td>£51,215</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>9,180</td>
<td>£34,363</td>
</tr>
</tbody>
</table>

EPACT prescribing data from December 2015 to November 2016

Please note, clomipramine is licensed for indications other than cataplexy and is used an adjunct to other therapies when used to treat cataplexy - the prescribing data in the above table will not be solely representative of its use in treating cataplexy.

Extrapolating the prescribing data in the table above, approximately 243 patients were treated with modafinil in the year to November 2016 in Lancashire. Assuming the number of patients remains stable, if 10% of these patients were prescribed pitolisant in place of modafinil, the total number of patients treated would be:
- 24 patients treated with pitolisant
- 219 patients treated with modafinil.

The total cost to treat patients given a 10% switch to pitolisant would be:
- £92,016 to £349,680 for pitolisant (depending on dose)
- £46,094 for modafinil
- Total new spend = £138,110 to £395,774

The extra spend in one year because of 10% uptake of pitolisant will be:

£138,110 to £395,774 – £51,215 = £86,895 to £344,559

Innovation, need, equity:

Pitolisant offers another treatment option in patients with narcolepsy with/without cataplexy where there are currently few safe and well tolerated treatments.

References


### Grading of evidence (based on SORT criteria):

<table>
<thead>
<tr>
<th>Levels</th>
<th>Criteria</th>
<th>Notes</th>
</tr>
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<tbody>
<tr>
<td><strong>Level 1</strong></td>
<td>Patient-oriented evidence from:</td>
<td>High quality individual RCT = allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)</td>
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<tr>
<td></td>
<td>• high quality randomised controlled trials (RCTs) with low risk of bias</td>
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<td>• systematic reviews or meta-analyses of RCTs with consistent findings</td>
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<tr>
<td><strong>Level 2</strong></td>
<td>Patient-oriented evidence from:</td>
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<tr>
<td></td>
<td>• clinical trials at moderate or high risk of bias</td>
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<td>• systematic reviews or meta-analyses of such clinical trials or with inconsistent findings</td>
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<td>• cohort studies</td>
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<td>• case-control studies</td>
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<tr>
<td><strong>Level 3</strong></td>
<td>Disease-oriented evidence, or evidence from:</td>
<td>Any trial with disease-oriented evidence is Level 3, irrespective of quality</td>
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<tr>
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<td>• consensus guidelines</td>
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<td>• expert opinion</td>
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<td>• case series</td>
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