East Surrey CCG, Guildford & Waverley CCG, North West Surrey CCG, Surrey Downs CCG, Surrey Heath CCG, Crawley CCG, Horsham & Mid-Sussex CCG

Evidence review for Prescribing Clinical Network

Medicine details	
Name, brand name	Pitolisant (Wakix®)
Manufacturer	Lincoln Medical Limited
Proposed indication	Narcolepsy with or without cataplexy in adults
Requested by	Queen Victoria Hospital NHS Foundation Trust (QVH) Recommendation RED – suitable for prescribing and supply by Specialist Sleep Centres only

SUMMARY

Clinical Effectiveness

Pitolisant is the first of a new class of drug – a histamine H3-receptor antagonist/inverse agonist licensed to treat narcolepsy with or without cataplexy in adults. It is a potent, orally active agent which enhances the activity of histaminergic neurons in the brain. It crosses the blood-brain barrier and elicits histamine release across the central nervous system accompanied by the release of wake promoting neurotransmitters (such as dopamine, noradrenaline and acetylcholine) (1). In patients suffering from narcolepsy with or without cataplexy, pitolisant improves the level and duration of wakefulness and daytime alertness assessed by objective measures of ability to sustain wakefulness (e.g. Maintenance of Wakefulness Test (MWT)) and attention (e.g. Sustained Attention to Response Task (SART)) (2). 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.

According to recent NICE evidence studies:

- The clinical effectiveness of Pitolisant 10 mg to 40 mg per day was statistically and clinically superior to placebo for improving excessive daytime sleepiness measured by the Epworth Sleepiness Scale (ESS) (3)
- Pitolisant 10 mg to 40 mg per day was not shown to be non-inferior to modafinil 100 mg to 400 mg per day for excessive daytime sleepiness measured by the ESS (3)
- For time awake in a darkened room, pitolisant 10mg to 40 mg per day was statistically superior to placebo and there was no statistically significant difference compared with modafinil 100 mg to 400 mg per day measured by the maintenance of wakefulness test (3)
- For attention level, there was no statistically significant difference between pitolisant 10 mg to 40 mg per day and placebo, or pitolisant 10 mg to 40 mg per

day 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) (3)

Pitolisant 5 mg to 40 mg per day reduced the weekly cataplexy rate by about half compared with placebo; 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 (7-week duration, n=106) (4).

As pitolisant has been given a new medicine status from NICE, a complete tolerability and improvement outcome document has not yet been produced. All information gathered has been done so with the aid of NICE evidence summary, the product manufacturer and anecdotal data from esteemed colleagues within this niche field of medicine. These findings will be discussed throughout this report.

Safety

Pitolisant is subject to additional monitoring however, The European Public Assessment Report (EPAR) (5) 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 (6).

Summary of the safety profile

The most frequent adverse drug reactions (ADRs) reported with pitolisant were 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%), upper abdominal pain (0.9%). The most serious ADRs are abnormal weight decrease (0.09%) and spontaneous abortion (0.09%) (2).

Special populations

Elderly

In 68 to 80 years old patients the pharmacokinetics of pitolisant is not different compared to younger patients (18 to 45 years of age). Above 80 years old, kinetics shows a slight variation without clinical relevance. Limited data are available in elderly. Therefore, dosing should be adjusted according to their renal hepatic status (see below).

Hepatic and Renal

Pitolisant is contraindicated in people with severe hepatic impairment and should be administered with caution in people with moderate hepatic or renal impairment. The dose should be adjusted accordingly (See summary of product characteristics for pitolisant).

Psychiatric disorders

Pitolisant should be administered with caution in patients with history of psychiatric disorders such as severe anxiety or severe depression with suicidal ideation risk.

Gastrointestinal disorders

Gastric disorders reactions have been reported with pitolisant. Therefore it should be administered with caution in patients with acid related gastric disorders (please see Table 1 below for further information) or when co-administered with gastric irritants such as corticosteroids or NSAID.

Nutrition disorders

Pitolisant should be administered with caution in patients with severe obesity or severe anorexia. In case of significant weight change, treatment should be re-evaluated by the physician.

Cardiac disorders

There is a risk of mild to moderate prolongation of QTc interval with supra-therapeutic doses of pitolisant (3 to 6 times the therapeutic dose that is 108 mg to 216 mg). Therefore caution is required in people with cardiac disease; those taking other QT-prolonging medicines or products known to increase the risk of repolarization disorder and should be monitored carefully.

Epilepsy

Convulsions were reported at high doses in animal models. In clinical trials, aggravation was reported in one epileptic patient. Caution should be taken for patients with severe epilepsy.

Women of childbearing potential

Women of childbearing potential have to use effective contraception during treatment and at least up to 21 days after treatment discontinuation (based on pitolisant/metabolites half-life). 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.

Drug-drug interactions

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. Those taking medicines that are known to increase pitolisant levels (for example CYP2D6 inhibitors, such as paroxetine) should be used and monitored with caution.

Rebound effect

No rebound effect was reported during clinical trials. However, treatment discontinuation should be monitored.

The following adverse reactions have been reported with pitolisant during clinical studies enrolling more than 1094 patients in narcolepsy and other indications and are listed below; within each frequency group, adverse reactions are presented in order of decreasing seriousness:

	Common	**Uncommon**	**Rare**
Infections and infestations		Sweating	
Metabolism and nutrition disorders		Decreased appetite Increased appetite Fluid retention	Anorexia Hyperphagia Appetite disorder
Psychiatric disorders	Insomnia Anxiety Irritability Depression Sleep disorder	Agitation Hallucination Hallucination visual, auditory Affect lability Abnormal dreams Dyssomnia Middle insomnia Initial insomnia Terminal insomnia Nervousness Tension Apathy Nightmare Restlessness Panic Attack Libido decreased Libido increased	Abnormal behaviour Confusional state Depressed mood Excitability Obsessive thoughts Dysphoria Hypnopompic hallucination Depressive symptom Hypnagogic hallucination Mental impairment
Nervous system disorders	Headache Dizziness Tremor	Dyskinesia Balance disorder Cataplexy Disturbance in attention Dystonia On and off phenomenon Hypersomnia Migraine Psychomotor hyperactivity Restless Legs Syndrome Somnolence Epilepsy Bradykinesia Paresthesia	Loss of consciousness Tension headache Memory impairment Poor sleep quality

Eye disorders		Visual acuity reduced Blepharospasm	
Ear and labyrinth disorders	Vertigo	Tinnitus	
Cardiac disorders		Extrasystoles Bradycardia	
Vascular disorders		Hypertension Hypotension Hot flush	
Respiratory, thoracic and mediastinal disorders		Yawning	
Gastrointestinal disorders	Nausea Vomiting Dyspepsia	Dry mouth Abdominal pain Diarrhoea Abdominal discomfort Abdominal pain upper Constipation Gastroesophageal reflux disease Gastritis Gastrointestinal pain Hyperacidity Paraesthesia oral Stomach discomfort	Abdominal distension Dysphagia Flatulence Odynophagia Enterocolitis
Skin and subcutaneous tissue disorders		Erythema Pruritus Rash Hyperhidrosis	Toxic skin eruption Photosensitivity
Musculoskeletal and connective tissue disorders		Arthralgia Back pain Muscle rigidity Muscular weakness Musculoskeletal pain Myalgia Pain in extremity	Neck pain Musculoskeletal chest pain
Renal and urinary disorders		Pollakiuria	
Pregnancy, puerperium and perinatal conditions			Abortion spontaneous

Reproductive system and breast disorders		Menorrhagia	
General disorders and administration site conditions	Fatigue	Asthenia Chest Pain Feeling Abnormal Malaise Oedema Peripheral oedema	Pain Night sweats Sense of oppression
Investigations		Weight increased Weight decreased Hepatic enzymes increased Electrocardiogram QT prolonged Heart rate increased Gamma- glutamyltransferase increased	Creatine phosphokinase increased General physical condition abnormal Electrocardiogram repolarisation abnormality Electrocardiogram T wave inversion

Table 1 – Tabulated list of adverse reactions based on SPC for Pitolisant (2)

The EPAR discusses that the long-term safety data for pitolisant in people with narcolepsy are limited. In HARMONY III (an unpublished open-label, 12-month safety study) (7) 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. 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 table 2 and 3 below.

In HARMONY I the most frequent adverse events were headache, insomnia, abdominal discomfort and nausea for the pitolisant group. Serious adverse events occurred in 1 person in the pitolisant group (abdominal pain). No participants in the placebo or pitolisant group had withdrawal syndrome during the withdrawal phase.

	Pitolisant	**Modafinil**	**Placebo**	**Analysis**
Population size	**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

Table 2 – Overview of results for safety and tolerability of Pitolisant in HARMONY I (3)

In HARMONY-CTP, the most frequent adverse events were headache, irritability, anxiety and nausea. Severe adverse events occurred in 1 person in the pitolisant group (nausea). No participants in the pitolisant group had withdrawal syndrome during the withdrawal phase.

	Pitolisant	**Placebo**	**Analysis**
Population size	**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

Table 3 – Overview of results for safety and tolerability of Pitolisant in HARMONY-CTP (4)

Patient factors

Pitolisant is on the 2019/20 National Tariff Payment System: list for tariff exclusion. This was added in April 2019. NHS England has published V14 of the drug list and NHS England is not denoted as the responsible commissioner for pitolisant. Currently, NHS England commission sodium oxybate in children up until their 19th birthday. However, once the patient reaches 19 years of age, commissioning responsibility then falls to an individual CCG. It is expected that commissioning arrangements for pitolisant will be in line with sodium oxybate. The Regional Medicines Optimisation Committee feel that the prescribing of sodium oxybate in adults fits the criteria for classification of a specialised service, and that a request could be put forward in order to change the commissioning pathway. This may affect who commissions medications for adult sleep services in the future.

Sodium oxybate does not have a NICE Technology Appraisal, but is currently commissioned by all the CCGs in Sussex and Surrey as a local agreement. As pitolisant is payment by results excluded (PbRe), then the CCGs will need to consider whether they agree to fund in the absence of a NICE Technology Appraisal. NICE do not have pitolisant in the pipeline for review. Due to the cost of drug treatment, activity costs would not cover acute trust expenditure.

The Regional Medicines Optimisation Committee is currently reviewing sodium oxybate in relation to developing a commissioning framework to support CCG decision making. It was clarified that the Committee were not being asked to advise for or against the use of sodium oxybate in adults. Additionally, NHSE specialised commissioning will work with specialists in the treatment of narcolepsy in adults and in children to produce a document to facilitate the transition of paediatric patients to adult services.

Due to the nature of the condition being treated, most patients do not hold a UK driving license due to strict DVLA regulations surrounding narcolepsy. Queen Victoria Hospital as a tertiary centre manages patients across a wide geographical footprint. Review

appointments are usually conducted by telephone which attracts a lower tariff. If pitolisant is commissioned then delivery options will be explored with Homecare providers to further facilitate supply options to this patient group.

Due to the nature of its formulation and dosing schedule, this medicine will be straight forward to take from a patient perspective – orally once daily after breakfast as opposed to twice at night like sodium oxybate. Pitolisant has also shown to have the best safety profile in a multiple treatment comparison and the highest benefit/risk ratio as per a recently published study (8). It is less likely to be abused and would be viewed a more desirable treatment option from a patient's viewpoint; when compared against sodium oxybate (which is also last line therapy for this indication - see figure 1 below for proposed treatment pathway).

As pitolisant is not a Controlled Drug it would be easier for the patient to be given a longer supply (once established on this therapy) per dispensing as it would not come under CD supply regulations (DoH strongly recommends no more than a 30 day supply be given for schedule 2 or 3 controlled drugs).
It is proposed this medicine to be given RED status initially – "Hospital only" within Sleep Centres until a sufficient safety and side effect profile has been established. Pitolisant has been approved for use at Guy's and St Thomas's Hospital as another tertiary sleep centre.

This medicine does not represent a cost saving when compared to the current sleep Pathway, as it is an alternative line of therapy, but it is advantageous for clinicians and patients as it offers an additional last line of therapy that has a different pharmacokinetic profile compared with sodium oxybate. The addition of pitolisant to the treatment pathway would be consistent with treatments offered at neighbouring sleep centres (e.g. SEL), and is cost effective when compared with sodium oxybate (see cost comparison below).

Cost implications

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 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 (9).

Currently all medications denoted in the sleep pathway are prescribed, monitored and managed by the Tertiary centre.

Table 4 below compares the comparative costs of treatment

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	100mg tablets: £2.20 – £8.80 200mg tablets: £4.50 - £9.00
Methylphenidate immediate release tablets	10 mg to 60 mg (usually 20 mg to 30 mg) daily in divided doses before meals	10mg tablets: £2.98 - £17.88 20mg tablets: £6.00 - £18.00
Methylphenidate modified release capsules	10 mg to 60 mg (usually 20 mg to 30 mg) daily in divided doses before meals	10mg capsules: £18.03- £108.18 30mg capsules: £25.25 - £50.50 60mg capsules: £50.49
Methylphenidate modified release tablets	10 mg to 60 mg (usually 20 mg to 30 mg) daily in divided doses before meals	18mg tablets: £3.85 - £11.55 36mg tablets: £5.20 - £11.40 54mg tablets: £6.00
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	5mg tablets: £16.50 - £198
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	500mg/ml: £540 [d] - £1,080

	2 weeks to a maximum of 9 g daily in 2 divided doses	

Table 4 – Comparative costs of pharmaceutical treatments from QVH suppliers

[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). *Potential PAS option- initial 3 months of treatment free of charge

[d] 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).

Relevant guidance / reviews

Currently, there are no relevant recommendations or conclusions from NICE aside from the evidence summary published in March 2017. Due to this medicine holding a new drug status, it is expected that guidelines will be published nationally in years to come once the exposure to this drug has been increased across the country in varying sleep centres. Pitolisant is not in the NICE pipeline for review.

The Sleep Centre at QVH will incorporate pitolisant into the clinical audit programme, outlining:
- The total number of patients started on pitolisant for the treatment of narcolepsy (with or without cataplexy) and the numbers continuing treatment
- Patient related outcomes, including:
(i) Response to treatment [to include effect on ESS scores]
(ii) adverse effects
(iii) number of withdrawals from treatment and the reasons for withdrawal
- Any impact on hospital activity, including follow up appointments

Likely place in therapy relative to current treatments

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/unlicensed 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.(2)

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 (13). Sodium oxybate is a schedule 2 Controlled Drug with requirements around supply, possession, prescribing, and record keeping.

Pitolisant is being requested for the treatment of narcolepsy with or without cataplexy as a last line treatment option. The evidence base for pitolisant was stronger in the single agent setting, but clinical experience from Guys and St Thomas Foundation NHS Trust suggests both monotherapy and combination therapy is effective in clinical practice.

Figure 1 below shows the treatment pathway for the pharmacological management of narcolepsy at QVH and GSTT sleep centres.

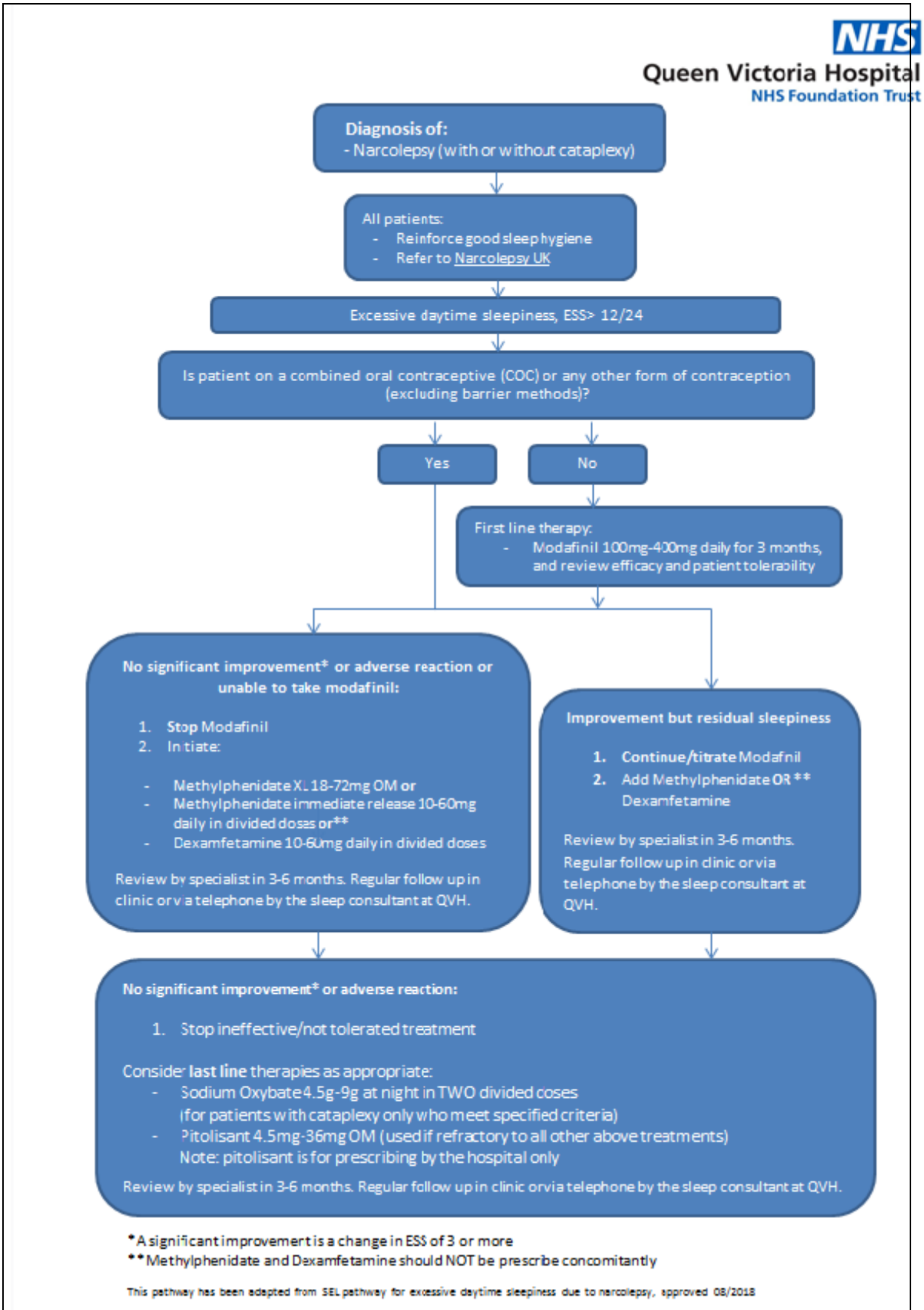

Figure 1 – Pathway for the pharmacological management of excessive daytime sleepiness due to narcolepsy

Recommendation to PCN
Recommendation RED status –for the treatment of narcolepsy with or without cataplexy as a last line treatment option. Suitable for prescribing and supply at specialist Sleep Centres only. Commissioners to fund as a PbRe medication via the blueteq system. Recommend reviewing the status of this medicine in 2 years-time, once sufficient clinical and safety data has been obtained, which may allow future conversations about transfer of care under an effective shared care agreement.

Medicine details – taken from SPC (1)	
Name and brand name	Pitolisant (Wakix®)
Licensed indication, formulation and usual dosage	• Licensed for the treatment of narcolepsy with or without cataplexy in adults • Available as a 4.5mg and 18mg film-coated tablet formulation only • Pitolisant 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.
Summary of mechanism of action, and relevant pharmacokinetics	**<u>Mechanism of action</u>** Pitolisant is a potent, orally active histamine H3-receptor antagonist/inverse agonist which, via its blockade of histamine auto-receptors enhances 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 (1).

Pharmacokinetics

Absorption

Pitolisant is well and rapidly absorbed with peak plasma concentration reached approximately three hours after administration.

Distribution

Pitolisant exhibits high serum protein binding (>90%) and demonstrates approximately equal distribution between red blood cells and plasma.

Biotransformation

The metabolism of pitolisant in humans is not completely characterised. The available data show that the major non-conjugated metabolites are hydroxylated derivatives in several positions. The 5- aminovaleric acid is the major phase I inactive metabolite and is found in urine and serum. It is formed under the action of CYP3A4 and CYP2D6. Several conjugated metabolites were identified, the major ones (inactive) being a glycine conjugate of the acid metabolite of O-dealkylated desaturated pitolisant and a glucuronide of a ketone metabolite of monohydroxy desaturated pitolisant.

On liver microsomes, pitolisant does not significantly inhibit the activities of the cytochromes CYP1A2, CYP2C9, CYP2C19, CYP2C8, CYP2B6, CYP2E1 or CYP3A4 and of uridine diphosphate glucuronosyl transferases isoforms UGT1A1, UGT1A4, UGT1A6, UGT1A9 and UGT2B7 up to the concentration of 13.3 µM, a level considerably higher than the levels achieved with therapeutic dose. Pitolisant is an inhibitor of CYP2D6 with moderate potency (IC_{50} = 2.6 µM).

Pitolisant induces CYP3A4, CYP1A2 and CYP2B6 *in vitro*. Clinically relevant interactions are expected with CYP3A4 and CYP2B6 substrates and by extrapolation, UGTs, CYP2C and P-gp substrates.

In vitro studies indicate that pitolisant is neither a substrate nor an inhibitor of human P-glycoprotein and breast cancer resistance protein (BCRP). Pitolisant is not a substrate of OATP1B1, OATP1B3. Pitolisant is not a significant inhibitor of OAT1, OAT3, OCT2, OATP1B1, OATP1B3, MATE1, or MATE2K at the tested concentration. Pitolisant shows greater than 50% inhibition towards OCT1 (organic cation transporters 1) at 1.33 µM, the extrapolated IC_{50} of pitolisant is 0.795 µM.

	Elimination Pitolisant has a plasma half-life of 10-12 hours. Upon repeated administrations, the steady state is achieved after 5-6 days of administration leading to an increased serum level around 100%. Inter individual variability is rather high, some volunteers showing outlier high profile (without tolerance issues). The elimination is mainly achieved via urine (approximately 63%) through an inactive non conjugated metabolite and a glycine conjugated metabolite. 25% of the dose is excreted through expired air and a small fraction (<3%) recovered in faeces where the amount of pitolisant or was negligible.
Important drug interactions	Antidepressants Tri or tetracyclic antidepressants (e.g. imipramine, clomipramine, mirtazapine) may impair the efficacy of pitolisant because they display histamine H1-receptor antagonist activity and possibly cancel the effect of endogenous histamine released in brain by the treatment. Anti-histamines Anti-histamines (H1-receptor antagonists) crossing the haemato-encephalic barrier (e.g. chlorpheniramine, diphenydramine, promethazine, mepyramine) may impair the efficacy of pitolisant. QT-prolonging substances or known to increase the risk of repolarization disorders Combination with pitolisant should be made with careful monitoring. Pharmacokinetic interactions *Medicinal products affecting pitolisant metabolism* - Enzyme inducers Co-administration of pitolisant with rifampicin in multiple doses significantly decreases pitolisant. Therefore, co-administration of pitolisant with potent CYP3A4 inducers (e.g. rifampicin, phenobarbital, carbamazepine, phenytoin) should be done with caution. With St John's Wort (Hypericum Perforatum), due to its strong CYP3A4 inducing effect, caution should be exercised when taken concurrently with pitolisant. A clinical monitoring should be made when both active substances are combined and, eventually a dosage adjustment during the combination and one week after the inducer treatment. - CYP2D6 inhibitors

	Co-administration of pitolisant with paroxetine significantly increases pitolisant. Given the 2-fold increase of pitolisant exposure, its co-administration with CYP2D6 inhibitors (e.g. paroxetine, fluoxetine, venlafaxine, duloxetine, bupropion, quinidine, terbinafine, cinacalcet) should be done with caution. A dosage adjustment during the combination could eventually be considered. ***Medicinal products that pitolisant may affect metabolism*** - CYP3A4 and CYP2B6 substrates Based on *in vitro* data, pitolisant and its main metabolites may induce CYP3A4 and CYP2B6 at therapeutic concentrations. No clinical data on the magnitude of this interaction are available. Therefore, the combination of pitolisant with substrates of CYP3A4 and having a narrow therapeutic margin (e.g. immunosuppressants, docetaxel, kinase inhibitors, cisapride, pimozide, halofantrine) should be avoided. With other CYP3A4, CYP2B6 (e.g. efavirenz, bupropion), CYP2C (e.g. repaglinide, phenytoin, warfarin), P-gp (e.g. dabigatran, digoxin) and UGT (e.g. morphine, paracetamol, irinotecan) susbtrates, caution should be made with a clinical monitoring of their efficacy. With oral contraceptives, the combination with pitolisant should be avoided and a further reliable contraceptive method used. - Substrates of OCT1 Pitolisant shows greater than 50% inhibition towards OCT1 (organic cation transporters 1) at 1.33 µM, the extrapolated IC_{50} of pitolisant is 0.795 µM. Even if the clinical relevance of this effect is not established, caution is advised when pitolisant is administered with a substrate of OCT1 (e.g. metformin (biguanides)). Paediatric population Interaction studies have only been performed in adults.
Monitoring requirements	Drug therapy will be routinely monitored every 3-6 months to establish whether it is providing clinical benefit to the patient. This will be measured against the Epworth Sleepiness Scale (ESS). A clinically significant improvement would be indicated by a change in Epworth Sleepiness Scale (ESS) of 3 or more (from baseline) following treatment with pitolisant. It will take 3 to 6 months to establish if the drug is beginning to work in the patient and if necessary whether a dose increase/reduction is required.

	However, if the patient does not achieve a 3 point reduction from baseline after the initial 3 months then treatment will be stopped. If the patient demonstrates a partial response, then a further 3 months treatment to be considered. Funding will be approved on an annual basis thereafter and will only be continued if the patient maintains or improves on the 3 point reduction from baseline. Desired treatment benefits would allow the patient to achieve a better quality of life and less residual day-time sleepiness as a result of their disorder. Patients will also be monitored for signs of toxicity e.g. abnormal changes to baseline observations such as heart rate and blood pressure, and in addition will be encouraged to report any signs of adverse effects to QVH sleep centre – in order to collate further safety data for this medicine.
Prescribing considerations	Recommendation RED status –for the treatment of narcolepsy with or without cataplexy as a last line treatment option. Suitable for prescribing and supply at specialist Sleep Centres only. Commissioners to fund as a PbRe medication via the blueteq system. Once daily administration- dose titration required dependent on clinical response. Pitolisant is a black triangle medicine i.e. as it is a new medicine; it is under additional monitoring to allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions to the MHRA via the Yellow Card scheme.
Other considerations	Clinicians will be following the pharmacological pathway for the management of narcolepsy (please see figure 1 above). Pitolisant will only be initiated should the patient be intolerant to all other therapies or if previous therapy has proved ineffective. In addition to the above, QVH proposed to audit the use of this medicine in order to determine which groups of patients are receiving this therapy and if it is proving effective in this indication. It is planned that audit results will be published in order to support treatment approaches in Narcolepsy in the future.

Potential patient group (if appropriate to include)	
Brief description of disease	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 (9). 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 (9) (14). The drug manufacturing 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 in the UK over a 5-year period (source: Lincoln Medical Ltd, October 2016)(15).
Potential patient numbers per 100,000	The Sleep Centre at QVH estimates 8 – 9 patients will be eligible for treatment with pitolisant each year. Approximately a third of the patients identified are from the South of England. As per patient population data obtained from 22 CCG's* along the South Coast of the UK, we currently serve a patient population of ~ 4,000,000 people. It is estimated that 1,600 patients from this population will suffer from narcolepsy. * Unable to obtain patient population data for 5 CCG's which included: NHS Thanet, South-East commissioning hub, South-East H&J commissioning hub, Kent, Surrey and Sussex commissioning hub and High Weald Lewes Havens
Outcomes required	A clinically significant improvement would be indicated by a change in Epworth Sleepiness Scale (ESS) of 3 or more (from baseline) following treatment with pitolisant. If the patient does not achieve a 3 point reduction from baseline after an initial 3 months of therapy then treatment will be stopped. If the patient demonstrates a partial response, then a further 3 months of treatment to be considered. Patients will only be continued if they maintain or improve on the 3 point reduction from baseline. Desired treatment benefits would allow the patient to achieve a better quality of life and less residual day-time sleepiness as a result of their disorder.

Summary of current treatment pathway

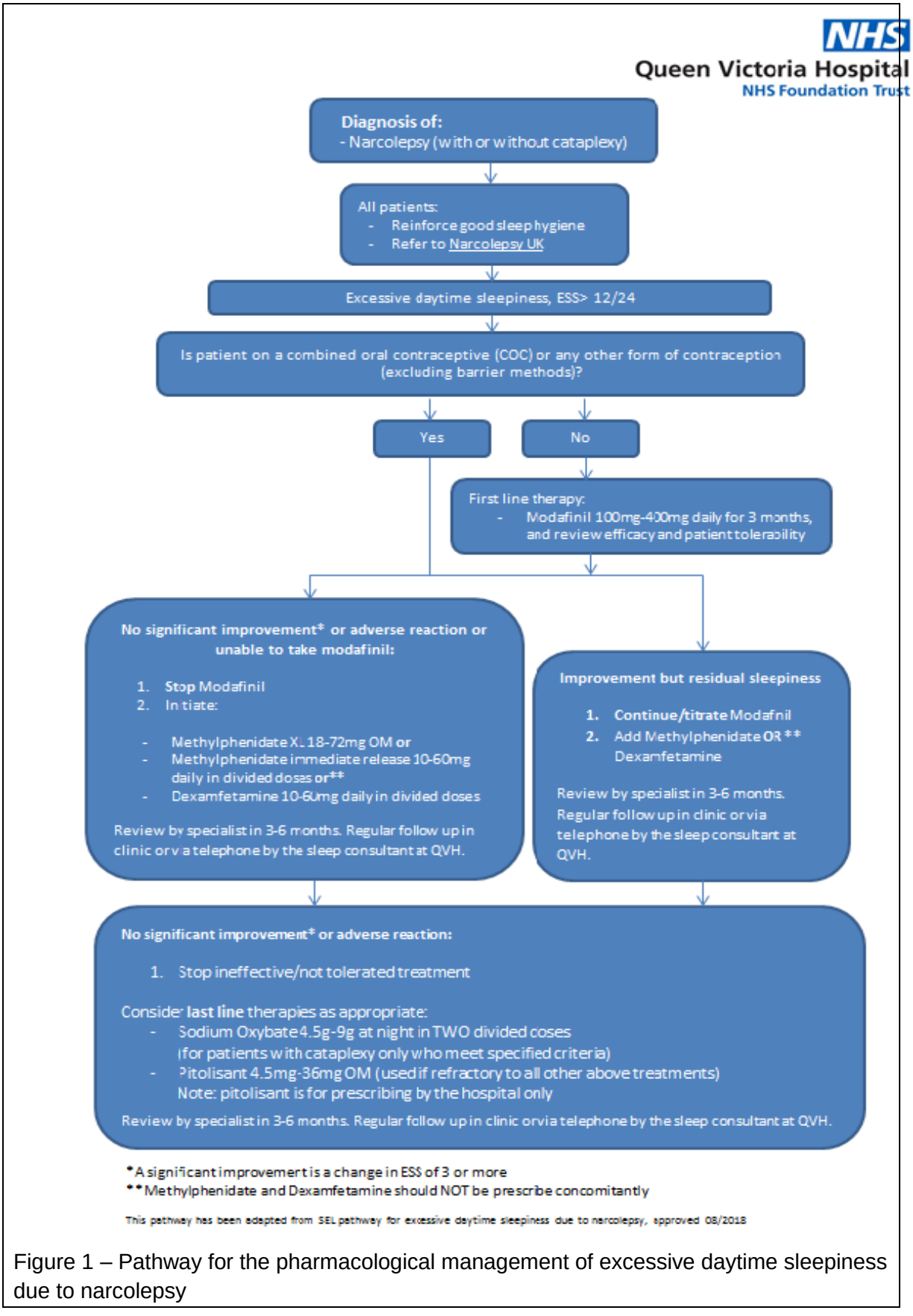

Figure 1 – Pathway for the pharmacological management of excessive daytime sleepiness due to narcolepsy

Evidence review

Currently, an evidence summary has been undertaken and completed by NICE. This can be found by accessing the following link below:

https://www.nice.org.uk/advice/es8/chapter/Evidence-review (6)

One particular sleep centre in the Midlands have a considerable amount of data surrounding the use of pitolisant in 150 patients, however, as the drug has been used in an off-license manner the results of these findings are not accurate for evaluation at this time. The results have also not been published or made publicly available for access.

Equity / Stakeholder views (if relevant)	
Decisions of local Trusts DTCs and neighbouring APCs	Guys and St Thomas NHS Foundation Trust. Pitolisant as monotherapy was approved on their trust formulary as a 'Red' drug with funding confirmed at Trust level. The Trust has been using pitolisant since May 2018, and their internal audit demonstrated that 50% of patients were non-responders at 3 months. The South East London Area Prescribing Committee has just reviewed the funding status for pitolisant and has provisionally agreed CCG funding pending minute approval. In addition, pitolisant was approved for combination treatment, and idiopathic hypersomnia. East Sussex Area Prescribing Committee has recently been asked to consider Pitolisant for formulary addition. The Committee noted that in clinical trials, pitolisant had been shown to be less effective than modafinil for the symptoms of excessive daytime sleepiness but more effective than placebo for symptoms of excessive daytime sleepiness and cataplexy symptoms. From a health economic perspective the case for pitolisant as a cost effective option was questioned. However, whilst clinical gains are small, this represents a worthwhile impact on patient's QOL. The decision has been deferred pending further investigation of a PAS price and clarity on an objective measure of response. Post meeting update- Negotiations with the manufacturers of Pitolisant are ongoing, but they are currently prepared to offer the first 3 months of treatment free.
Recommendations from national / regional decision making groups	Currently, there are nil recommendations or conclusions from NICE, SMC, MTRAC etc.
Stakeholder views	

	The consultants at QVH Sleep Centre have expressed an overwhelming interest and need to have the above named drug as part of their narcolepsy pathway. Being a specialist sleep centre QVH would need to remain at the “forefront” of their field in order to offer patient’s the most up-to-date therapy available. Patients suffering from narcolepsy who attend QVH have also expressed an interest in pitolisant as it would allow a larger scope of treatment options available as well as allow a “last-resort therapy” should all else fail or prove ineffective. Patients who are currently eligible for pitolisant are being referred to Guys and St Thomas’s Foundation Trust (GSTT). Patients who exhausted available treatment options prior to pitolisant being available were being offered experimental elements of care, whereby all available medicines within the differing pathways were being utilised to establish which provided best relief for symptoms. If the above pathways failed to prove effective, patients would have to remain sub-therapeutic on their current therapy and lifestyle interventions would have to be incorporated (such as day-time naps, addition of other unlicensed agents such as selegiline etc) with the aim of improving quality of life.
CCG priorities	Pitolisant is a PbRe medication but is not subject to a NICE TA and therefore the CCG is not mandated to fund. Currently patients are being referred to GSTT to access pitolisant which is not yet approved with the local commissioners. Some CCGs would agree to fund patients referred to GSTT under ‘non-contractual agreements’ thereby accepting the costs locally without any control over the use of pitolisant in an approved pathway or access to audit data for future consideration.

Health economic considerations	
Cost per year per patient	The Sleep Centre at QVH estimates 8 – 9 patients will be eligible for treatment with pitolisant each year. Approximately a third of the patients identified are from the South of England. Treatment with pitolisant costs £3,720 to £7,440 per patient per year (depending on dosage). It is estimated that this equates to medicines related costs of up to £67,000 per year. The estimated patient number is across 22 CCGs*.

<table>
<tr><td></td><td>Medicines related cost of treatment for 40 patients per a 100,000** population would equate to £149,000 to £298,000 (depending on dosage).

*Unable to obtain patient population data for 5 CCG's which included: NHS Thanet, South-East commissioning hub, South-East H&J commissioning hub, Kent, Surrey and Sussex commissioning hub and High Weald Lewes Havens.
** This figure has been extrapolated using the narcolepsy.org statistic of every 1 in 2,500 people suffering from narcolepsy in the UK.</td></tr>
<tr><td>Alternative treatments cost per patient per year</td><td>
<table>
<tr><th><u>Treatment Cost (Low dose)</u></th><th><u>Daily</u></th><th><u>Monthly</u></th><th><u>Yearly</u></th><th><u>Pitolisant annual Saving/Cost impact per patient</u></th></tr>
<tr><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Pitolisant* (18mg one tablet a day)</td><td>£10.33</td><td>£310</td><td>£3,720</td><td></td></tr>
<tr><td>Sodium Oxybate (4.5g/day)</td><td>£21.90</td><td>£657</td><td>£7,884</td><td>£4,164 cost saving</td></tr>
<tr><td colspan="5"></td></tr>
<tr><th><u>Treatment Cost (Max dose)</u></th><th><u>Daily</u></th><th><u>Monthly</u></th><th><u>Yearly</u></th><th><u>Pitolisant annual Saving/Cost impact per patient</u></th></tr>
<tr><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Pitolisant* (18mg two tablets a day)</td><td>£20.66</td><td>£620</td><td>£7,440</td><td></td></tr>
<tr><td>Sodium Oxybate (9g/day)</td><td>£27.07</td><td>£1,092</td><td>£13,104</td><td>£5,664 cost saving</td></tr>
</table>
*Potential PAS option- initial 3 months of treatment free of charge

The annual savings above are only applicable if Pitolisant is used instead of Sodium Oxybate. Some patients will require therapeutic trials of both agents which will increase treatment costs in this pathway as in essence pitolisant could represent an additional line of therapy.</td></tr>
<tr><td>Other financial considerations</td><td>None</td></tr>
<tr><td>Health economic data (if available)</td><td>This is not currently available as patient figures are too small to economically evaluate impact on the NHS; due to lack of data available.

One particular sleep centre in the Midlands have a considerable amount of data surrounding the use of pitolisant in 150 patients, however, as the drug has been used in an off-license manner the results of these findings</td></tr>
</table>

	are not accurate for evaluation at this time. The results have also not been published or made publicly available for access.

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Nil for Both

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VERSION CONTROL SHEET

Version	Date	Author	Status	Comment
v.1	02/05/19	Asia M Latif	Specialist Pharmacist	Internal consultation
v.2	27/06/19	Samieah Khan	Specialist Pharmacist	Comments incorporated from East Sussex APC, GSTT audit review and evaluation criteria. Potential PAS included
v.3	29/07/19	Michelle Barnard	Specialist Pharmacy Technician	Amended document in response to comments received

Comments on Evidence review for Prescribing Clinical Network