Shared Care Guideline

Pitolisant – Narcolepsy with and without cataplexy

Executive Summary

- **Indication:** Narcolepsy in adult patients with or without cataplexy.
- Initiated by a Consultant Sleep Physician or under the direct supervision of a Consultant Sleep Physician for patients with a definitive diagnosis of narcolepsy in whom other licensed or unlicensed treatment options have been tried and optimised and despite this treatment has failed to improve symptoms, not been tolerated or in patients in whom other treatment options are contraindicated.
- Before initiation of pitolisant, all treatment options will be discussed with patient and patient's G.P.
- **Dose:** Initially 9 mg with breakfast, titrating to 18mg od after one week and a maximum of 36mg od after a further week depending on response to therapy.
- *Dose will be communicated to GP, CCG Medicine Management Team and patient by Specialist Sleep Consultant.*
- **Efficacy Monitoring:** Specific monitoring for efficacy to be carried out by tertiary care on a regular basis.
- **If a patient fails to respond to pitolisant or has significant side effects, treatment will be stopped.** This will be communicated to the patient, their G.P. and the funding CCG.

The responsibilities of the hospital specialist, GP and patient for this Shared Care Guideline can be found within this document.

Sharing of care depends on communication between the specialist, GP and the patient or their parent/carer. The intention to share care should be explained to the patient and accepted by them. Patients are under regular follow-up and this provides an opportunity to discuss drug therapy. The doctor/healthcare professional who prescribes the medication has the clinical responsibility for the drug and the consequences of its use. Further information about the general responsibilities of the hospital specialist and GP can be found here

1 Scope

This guideline provides information relating to pitolisant and outlines the responsibilities of the general practitioner and the Respiratory Support and Sleep Centre at Papworth Hospital NHS Foundation Trust in the prescribing and monitoring of this medicine.

2 Aim

To provide clear and concise information to general practitioners in order that their patients with narcolepsy receive on-going safe and effective care using evidence based medicine, following evaluation by our Sleep Medicine Consultants and their team.

3 Introduction

- Narcolepsy occurs in 1 in 2500 subjects and is a chronic, debilitating, life-long neurological disease characterised by excessive daytime sleepiness with most frequent onset in the second and third decades of life.

- The severe and excessive daytime sleepiness (EDS) caused by narcolepsy usually leads to the patient seeking help and has a significant impact on daily functioning and quality of life. Patients with narcolepsy readily fall asleep in all situations including at work and at school. Due to the severe symptoms patients with narcolepsy are not allowed to drive until treated and symptoms abate. The drowsiness and sleepiness also has significant impacts on attention, the ability to concentrate, impairs memory and leads to automatisms. In narcoleptic patients with or without cataplexy, pitolisant improves the level and duration of wakefulness and daytime alertness assessed subjectively (Epworth sleepiness score) and by objective measures of ability to sustain wakefulness (Maintenance of Wakefulness Test) and attention (Sustained Attention to Response Task).

- Narcolepsy usually progresses to include cataplexy (sudden loss of muscle tone), sleep paralysis, hypnagogic hallucinations and fragmented nocturnal sleep. Cataplexy affects approximately 75% of people with narcolepsy and is triggered by emotional stimuli such as anger, excitement or laughter. The severity of cataplexy ranges from dropping of the jaw or the head, to buckling of the legs. In secondary analyses Pitolisant has been shown to significantly reduce the frequency of cataplexy attacks in comparison to placebo.

- Pitolisant (Wakix) is licensed for the treatment of narcolepsy in adult patients with and without cataplexy. At Papworth Hospital NHS Foundation Trust pitolisant will be reserved for those narcolepsy patients whose EDS fails to respond to other wake promoting medicines e.g. modafinil, dexamphetamine and methylphenidate or in whom these medications are not tolerated or are contraindicated. The recommendation to start treatment will be made by Consultant only and the Consultant will be personally responsible for the decision to initiate pitolisant treatment.

- 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 use is associated with dose-related improvements in the symptoms of narcolepsy and reduction in the numbers of attacks of cataplexy. No withdrawal effects have been seen with pitolisant at therapeutic doses and its potential for abuse is less than that for other wake promoting medicines.

4 Abbreviations

- **CCG** = Clinical Commissioning Group
- **CNS** = Central Nervous System
- **RSSC** = Respiratory Support and Sleep Centre

5 Dose and Administration

- 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. Pitolisant is taken orally as a single dose in the morning during breakfast and is well absorbed reaching peak plasma concentrations within 3 hours (half-life 10-12 hours) and reaching steady state plasma concentration within 5-6 days.

Dose in hepatic and renal impairment:

- The elimination of pitolisant is mainly achieved via urine (approximately 63%) through an inactive non conjugated metabolite (BP2.951) and a glycine conjugated metabolite. 25% of the dose is excreted through expired air and a small fraction (<3%) recovered in faeces.
- In patients with moderate hepatic impairment (Child-Pugh B) two weeks after initiation of treatment, the daily dose can be increased without exceeding a maximal dose of 18 mg.
- Pitolisant is contra-indicated in patients with severe hepatic impairment (Child-Pugh C).
- No dosage adjustment is required in patients with mild hepatic impairment.
- In patients with renal impairment (CKD 2-4), the maximum daily dose should be 18 mg.

Special Populations:

- Safety and efficacy in children and adolescents has not been established therefore use in patients under 18 years of age is not recommended. Limited data in elderly patients therefore dose adjustment according to hepatic/ renal status.

Women of childbearing potential, Pregnancy and Breast Feeding:

- 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. Not advised in pregnancy or breast feeding.

Further information can be found in the Summary of Product Characteristics:
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002616/WC500204746.pdf

6 Adverse Effects

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%), abdominal pain upper (0.9%). The most serious ADRs are abnormal weight decrease (0.09%) and abortion spontaneous (0.09%).

Further information can be found in the Summary of Product Characteristics:
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002616/WC500204746.pdf

7 Cautions

- 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.
- Hepatic or renal impairment: Pitolisant is not known to cause hepatic or renal impairment and no specific monitoring is required. Pitolisant should be administered with caution in patients with either renal impairment or moderate hepatic impairment (Child-Pugh B) and dosing regimen should be adapted (see section 5).
- Gastrointestinal disorders: Gastric disorders reactions have been reported with pitolisant, therefore it should be administered with caution in patients with acid related gastric disorders 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: In two dedicated QT studies, supra-therapeutic doses of pitolisant (3-6-times the therapeutic dose, that is 108 mg to 216 mg) produced mild to moderate prolongation of QTc interval (10-13 ms). In clinical trials, no specific cardiac safety signal was identified at therapeutic doses of pitolisant. Nevertheless, patients with cardiac disease, co-medicated with other QT-prolonging medicinal products or known to increase the risk of repolarization disorders, or co-medicated with medicinal

products that significantly increase pitolisant Cmax and AUC ratio or patients with severe renal or moderate hepatic impairment should be carefully monitored.

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

Further information can be found in the Summary of Product Characteristics:
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002616/WC500204746.pdf

Rebound effects and withdrawal syndrome

- No evidence of rebound effects or withdrawal syndrome was reported in clinical trials however withdrawal should be monitored.

8 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed.
- Severe hepatic impairment (Child-Pugh C).
- Pregnancy or Breastfeeding.

Further information can be found in the Summary of Product Characteristics:
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002616/WC500204746.pdf

9 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. pheniramine maleate, 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 a careful monitoring.
- **Pharmacokinetic interactions**

  Medicinal products affecting pitolisant metabolism:

  Enzyme inducers: Co-administration of pitolisant with rifampicin in multiple doses significantly decreases pitolisant mean Cmax and AUC ratio about 39% and 50%, respectively. 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 mean Cmax and AUC0—72h ratio about 47% and 105%, respectively. Given the 2-fold increase of pitolisant exposure, its coadministration 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 and by extrapolation, CYP2C, UGTs and P-gp. 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.

Further information can be found in the Summary of Product Characteristics:
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002616/WC500204746.pdf

10 Monitoring Standards & Actions to take in the event of abnormal test results/symptoms

- Laboratory tests are not required to monitor patient response to pitolisant administration.

11 Shared Care Responsibilities

a. Hospital specialist:
The patients will be assessed by one of the consultants (Dr I E Smith, Dr T Quinnell, Dr M Davies, Dr N Oscroft and Dr M Mason). If the patient meets the commissioning criteria for pitolisant and is in agreement with the treatment plan then the hospital will undertake to:

- Ensure that an agreement to accept prescribing responsibility has been obtained from the general practitioner before treatment is initiated.

- Communicate any potential effects on co-morbidities and interactions with existing medication to the GP.
- Evaluate patients for a history of drug abuse and account for any additional risks in these patients.
- Provide information to the patient regarding the medicine.
- Where relevant, counsel the patient on the need for contraception, and confirm to the GP that this discussion has taken place.
- Provide the first 8 weeks supply of pitolisant.
- Recommend an initial dose and how this may be titrated according to the response to treatment.
- Inform the GP after each clinic attendance if there is any change to treatment or monitoring.
- Inform GP of patients who do not attend clinic appointments and discuss patient's on-going treatment plan.
- Review the patient's progress on treatment. If the patient has failed to respond to treatment after an four week period then pitolisant therapy will be discontinued.
- Be available for advice to the general practitioner.
- Answer patient enquiries on any aspect of this therapy.
- Review all treatment responders at an out-patient clinic 4 months after initiation of therapy and then again at an out-patient clinic 4 to 6 months later. Patients will then be seen every six months or annually as clinically indicated.
- Communicate all relevant information regarding treatment to the general practitioner.

b. General Practitioner:

- Continue to prescribe pitolisant once this has been initiated by the Respiratory Support and Sleep Centre consultant specialists.
- Communicate any adverse events or other problems with the medicine to the supervising consultant at Papworth Hospital.
- Request advice from the hospital specialist when necessary.

c. Patient or parent/carer:

- Report to the Consultant or GP if they do not have a clear understanding of their treatment.
- Patients must not exceed the recommended dose.
- Patients must attend their scheduled clinic appointments.
- Must inform other clinical staff that they are receiving treatment.
- Report any adverse effects to their Consultant or GP whilst taking pitolisant.
- Share any concerns they have in relation to treatment with pitolisant.
- Obtain their prescription from the same dedicated pharmacy of their own choice.

12 Contact numbers for advice and support

Papworth Hospital NHS Foundation Trust		
Specialist	**Post**	**Telephone** (direct lines)
Dr Ian E Smith	Director of RSSC and Consultant Sleep Physician	01480 364164
Dr Tim Quinnell	Consultant Sleep Physician	01480 364174
Dr Mike Davies	Consultant Sleep Physician	01480 364542
Dr Nick Oscroft	Consultant Sleep Physician	01480 364551

Dr Martina Mason	Consultant Sleep Physician	01480 364165
Mrs Netta Tyler	RSSC Directorate Pharmacist	01480 364762
Pharmacy Medicines Information Service		01480 364179
Pharmacy Medicines Helpline		01480 364739 (answerphone)

13 Equality and Diversity Statement

This document complies with the Papworth Hospital NHS Foundation Trust service Equality and Diversity statement.

14 Disclaimer

It is your responsibility to check that this printed out copy is the most recent issue of this document.

15 Document Management

Document ratification and history	
Approved by:	Papworth Thoracic Services Management Group
Date approved:	22 May 2017
Approved by:	Papworth Hospital Drugs and Therapeutics Committee
Date approved:	11 September 2017
Papworth number and version:	EJ045 v1
Submitted for ratification by:	Cambridgeshire and Peterborough Joint Prescribing Group
Date ratified:	22032018
Date placed on CPJPG website:	25042018
Review date:	2 years unless clinical evidence changes
Obsolete date:	
Supersedes which document?	N/A
Authors:	Netta Tyler RSSC Directorate Pharmacist
Owning Provider Trust:	Papworth Hospital NHS Foundation Trust
File name:	Shared Care Guideline: Pitolisant for the treatment of adult narcolepsy patients with and without cataplexy.
Version number:	1
Unique Reference No:	[JPG180322] Provided by C&P CCG MMT

The information contained in this guideline is issued on the understanding that it is accurate based on the resources at the time of issue. Further information can be found in the Summary of Product Characteristics:
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002616/WC500204746.pdf