South East London Integrated Medicines Optimisation Committee
Formulary recommendation

Reference	**061**
Intervention:	**Clonazepam/zopiclone/zolpidem for the management of restless legs syndrome (RLS)** (Clonazepam, zopiclone and zolpidem are sedative agents)
Date of Decision	**February 2017, updated March 2024 following RLS pathway update**
Date of Issue:	**March 2017, re-issued March 2024**
Recommendation:	**Amber 2 – initiation and minimum 3 months supply by the neurology specialist team (specialising in RLS)**
Further Information	• Clonazepam/zopiclone/zolpidem are accepted for use in line with the local pathway for the management of severe refractory restless legs syndrome (RLS). • Restless legs syndrome is often accompanied by unpleasant sensations, which may be painful in 30-50% of cases. Insomnia and poor sleep quality are also common complaints. • Clonazepam (0.25 –2mg at night) may be considered as a 2nd line option where there is failure to respond to or insufficient response* to first line therapies – dopamine agonists and gabapentin/pregabalin. • Either zopiclone (3.75 - 15mg at night) or zolpidem (5 - 10mg at night) may be considered as 2nd line treatment options for the management of insomnia in people with RLS. • The patient's first line therapy will be stopped before initiation of clonazepam or zopliclone or zolpidem. • These agents are not licensed for the management of RLS. This is an off label indication and patients should be made aware of this at time of initiation. • Treatment will be initiated and monitored by the neurology team (specialising in RLS). The neurology specialist team will regularly review patients for ongoing effectiveness of treatment. • The neurology specialist team will prescribe treatment for a **minimum of 3 months**. Prescribing will only be transferred to primary care when the therapy is confirmed as effective*, the patient is on a stable dose and has been confirmed to not be experiencing troublesome side-effects. • The neurology specialist team should provide the patient's GP with the SEL IMOC GP fact sheet about RLS and the medicines used to treat it and general information for the patient. • Clonazepam, zopiclone and zolpidem are schedule 4 (part 1) controlled drugs. • Prescribers should be aware of the risks associated with these agents, including falls, cognitive impairment, dependence and withdrawal symptoms. These risks will be considered by the neurology specialist team before these agents are initiated for RLS. *Effectiveness will be measured through the Epworth Sleepiness Scale (ESS) and the Restless Legs Syndrome Rating Scale (RLSRS).
Shared Care/ Transfer of care required:	No, however general information about RLS and the drugs used to treat it should be shared with the GP as part of the patient's individual management plan.
Cost Impact for agreed patient group	• If the prevalence of RLS is 3%, that 50% of patients present to healthcare systems for management and that 15% of those require drug therapy to treat symptoms this equates to 225 per 100,000 population. • If 20% of these patients do not respond adequately to dopamine agonists or alpha-2-delta ligands, and 50% of these are treated with benzodiazepines or hypnotics (the other 50% being treated with opioids) this equates to 23 patients per 100,000 population. • If clonazepam were the only benzodiazepine/hypnotic used, and an average dose of 2mg were required this equates to £2,500 per 100,000 population per annum.

	• These figures would be £690 and £345 per 100,000 population per annum for zopiclone and zolpidem respectively. • For SEL this would result in a cost of up to £51,000 per year. However, some of this will be a substitution for the dopamine agonists/gabapentin/pregabalin.
Usage Monitoring & Impact Assessment	**Acute Trusts:** • Monitor use and submit usage data and audit reports (against this recommendation and the pathway) upon request to the SEL IMOC
	SEL Borough Medicines Optimisation Teams: • Monitor ePACT2 data and exception reports from GPs if inappropriate prescribing requests are made to primary care.
Evidence reviewed	**References (from evidence evaluation)** 1. Garcia-Borreguero, D. and Williams, A. An update on restless legs syndrome (Willis-Ekbom disease): clinical features, pathogenesis and treatment. Current Opinions in Neurology 2014 27(4), 493-501. 2. Allen, R., et al. (2014a) Restless legs syndrome/Willis-Ekbom disease diagnostic criteria: updated International Restless Legs Syndrome Study Group (IRLSSG) consensus criteria-history, rationale, description, and significance. Sleep Medicine 15 (8), 860-873. 3. Nagandla, K. and De, S. (2013) Restless legs syndrome: pathophysiology and modern management. Postgraduate Medical Journal 89 (1053), 402-410. 4. Leschziner, G. and Gringas, P. (2012) Restless legs syndrome. BMJ 344 (), e3056. 5. Garcia-Borreguero, D., Ferini-Strambi, L., Kohnen, R. et al. (2012a) European guidelines on management of restless legs syndrome: report of a joint task force by the European Federation of Neurological Societies, the European Neurological Society and the European Sleep Research Society.European Journal of Neurology: The Official Journal of The European Federation of Neurological Societies 19 (11), 1385-96. 6. Hening W, Walters A, Allen R et al. Impact, diagnosis and treatment of restless legs syndrome (RLS) in a primary care population: the REST (RLS epidemiology, symptoms, and treatment) primary care study. Sleep Medicine 2004 p5237-5246 7. Stevens M. RLS/Willis-Ekborn disease morbidity: burden, quality of life, cardiovascular aspects, and sleep> Sleep Medicine Clinics 2015 10 p369-373 8. Clonazepam tablets, SPC. Available here. (accessed 02/09/2016) 9. Griffin C, Kaye A, Bueno F et al. Benzodiazepine Pharmacology and Central Nervous System–Mediated Effects. The Ochsner Journal 2013 13(2) p214-223 10. Drover D. Comparative pharmacokinetics and pharmacodynamics of short-acting hypno-sedatives: zaleplon, zolpidem and zopiclone. Clinical Pharmacokinetics 2004 43(4) p227-238. 11. Zopiclone tablets, SPC. Available here. (accessed 02/09/2016) 12. Zolpidem tablets, SPC. Available here. (accessed 02/09/2016) 13. Conti C, Olivera M, Saconato H et al. Benzodiazepines for restless legs syndrome (protocol). Cochrane Library. Available here. (accessed 02/09/2016) 14. Montagna P, Sassoli-de-Bianchi L, Zucconi M et al. Clonazepam and vibration in restless leg syndrome. Acta Neurologica Scandinavica 1984 69 p428-430. 15. Boghen D, Lamothe L, Elie R et al. The treatment of the restless legs syndrome with clonazepam: a prospective controlled study. Canadian Journal of Neurological Sciences 1986 13 p245-247. 16. Carlos K.; Carvalho .; Teixeira C et al. Benzodiazepines for restless legs syndrome: Cochrane review. Sleep, 2014, vol./is. 37/(A222), 0161-8105 17. Peled R, Lavie P. Double-blind evaluation of clonazepam on periodic leg movements in sleep. Journal of Neurology, Neurosurgery and Psychiatry 1987 50 p1679-1681. 18. Ohanna N, Peled R, Rubin A et al. Periodic leg movements in sleep: effect of clonazepam treatment. Neurology 1985 35 p408-411. 19. Shinno H, Oka Y, Otsuki M et al. Proposed dose equivalence between clonazepam and pramipexole in patients with restless legs syndrome. Progress in neuropsychopharmacology and biological psychiatry 2010 34(3) p522-526. 20. Buchfuhrer M. Strategies for the Treatment of Restless Legs Syndrome. Neurotherapeutics 2012 9 (4) p776-790. 21. KTT6 – Hypnotics. NICE 2016. Available here (accessed 02/09/2016)

NOTES:

a) SEL IMOC recommendations and minutes are available publicly via the website

b) This SEL IMOC recommendation has been made on the cost effectiveness, patient outcome and safety data available at the time. The recommendation will be subject to review if new data becomes available, costs are higher than expected or new NICE guidelines or technology appraisals are issued.

c) Not to be used for commercial or marketing purposes. Strictly for use within the NHS