Bromocriptine

REJECTED

The Expert Committee, after evaluation, declines to list the medicine proposed in the application.
The Model List of Essential Medicines reports reasons that Committee Members have identified for denying listing.

Section: 5. Medicines for diseases of the nervous system > 5.1. Antiseizure medicines

ATC codes: N04BC01

Indication	Parkinson disease ICD11 code: 8A00.0Z
INN	Bromocriptine
Medicine type	Chemical agent
List type	Core
Formulations	Oral > Solid: 2.5 mg ; 5 mg
EML status history	Application rejected in 2015 (TRS 994)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Patents have expired in most jurisdictions Read more about patents.
Wikipedia	Bromocriptine
DrugBank	Bromocriptine

Summary of evidence and Expert Committee recommendations

During the 19th meeting of the WHO Expert Committee in 2013, the Committee called for a detailed application for the addition of a dopamine agonist to the EML (1). Subsequently, an application reviewing the available evidence on oral dopamine agonists (bromocriptine, cabergoline, dihydroergocryptine mesylate, pramipexole, ropinirole) for the treatment of Parkinson disease was submitted by Dr Francesco Nonino, Drug Evaluation Unit and WHO Collaborating Centre in Evidence-Based Research Synthesis and Guideline Development, Emilia Romagna Health and Social Care Agency, Bologna, Italy. Expert reviews of the application were prepared by two members of the Expert Committee. No public comments were received in relation to the application. Parkinson disease (PD) is one of the commonest progressive neurodegenerative diseases in elderly people. The prevalence of PD varies from 30 to 180 per 100 000 population and increases with age in low-, middle- and high-income countries (2-5). The disease affects both males and females and is diagnosed in about 1.6% of people over the age of 65 years. The onset of PD is gradual and the disease evolves slowly: mean survival is more than 10 years. Diagnosis is primarily clinical and depends on the presence of a specific set of symptoms and signs, as well as on the response to drug therapy. The most common clinical manifestations are tremor at rest, rigidity, slowness of movement (bradykinesia) and poverty of movement (hypokinesia). Gait disturbances, postural instability and falls may develop. The Expert Committee acknowledged that: ■ Current pharmacological treatment is centred upon dopamine replacement to alleviate symptoms. ■ So far, no medicine has proved to be disease-modifying, stopping or reversing the neurodegenerative process that leads to PD. Motor symptoms therefore continue to progress and increasing doses of medication are required, resulting in short-term adverse effects and in medium- to long-term motor complications. ■ Most clinicians adopt the therapeutic strategy of delaying the start of pharmacological treatment until symptoms interfere with daily life. ■ The available pharmacological therapies for early-stage PD include levodopa, dopamine receptor agonists (DAs) and monoamine oxidase B inhibitors. Anticholinergics, beta-blockers and amantadine may be used in selected patients but are not generally recommended as drugs of first choice (6). ■ Starting drug treatment in the early stage of PD with either DAs or levodopa monotherapy has been

widely debated, since both approaches offer benefits and disadvantages. Postponing the introduction of levodopa gives the advantage of "shifting onwards" the occurrence of levodopa-related motor fluctuations and may give better control of motor symptoms for a longer period. Starting with levodopa may achieve a better tolerability and quality of life in the longer term. ■ Patients with advanced-stage PD require levodopa, and motor fluctuations are then inevitable. The mainstay of PD treatment is levodopa, the amino acid precursor of dopamine, combined with a peripheral dopa decarboxylase inhibitor; this has been the standard symptomatic therapy for PD for more than 40 years. The current EML lists levodopa+carbidopa as 100 mg+10 mg, 100 mg + 25 mg, and 250 mg + 25 mg. The main limitations of levodopa are its decreasing efficacy over time and the fluctuating responses to treatment. Use of DAs may offer some advantages in terms of lower occurrence of dyskinesia and motor fluctuations during the first 4-5 years of treatment. However their use is limited by a higher incidence of disabling non-motor adverse reactions. The older DAs – bromocriptine, pergolide, lisuride and dihydroergocryptine mesylate – are ergot derivatives, while ropinirole and pramipexole are nonergot derivatives. Lisuride and pergolide are not considered in this application, since the former is no longer available and the latter has been withdrawn for safety reasons. Most trials and systematic reviews investigated the benefit of use of DAs, distinguishing early-stage and advanced-stage PD, as stand-alone treatment or as adjunct to levodopa (7-12). When compared with placebo, DAs produced a significant improvement in symptom control in both early- and advanced-stage PD; however, when DAs were combined with levodopa and compared with levodopa and placebo, there was usually no difference observed between treatment arms at any time and with any scoring system (8, 9). Non-ergot long-acting DAs (e.g. extended-release pramipexole, prolonged-release ropinirole and transdermal rotigotine) consistently showed a significant benefit over placebo; comparison with levodopa, however, showed no significant differences for any outcome (11-12). A network meta-analysis of non-ergot DAs found that improvements with pramipexole and ropinirole were slightly less than with levodopa (10). The PD MED trial, a large, independent, pragmatic trial, compared early initiation with levodopa or initiation with a DA (i.e. ropinirole or pramipexole) in individuals with newly diagnosed PD (13). During 7 years of follow up, at no point was there any significant difference in quality of life, measured using the 39-item Parkinson Disease Questionnaire (PDQ-39) quality of life scale, between the levodopa arm and the DA arm., Average scores were consistently better among patients treated with levodopa, as were the average scores for the activities of daily living subscales. Improvements in quality-adjusted life-years were greater in the early-levodopa arm despite a higher proportion of patients suffering levodopa-related dyskinesias. Evidence concerning which class of add-on treatment is the more efficacious in advanced PD is lacking and there are uncertainties about differences in efficacy between DAs and other classes of drugs (e.g. catechol O-methyltransferase inhibitors (COMTI) and monoamine oxidase type B inhibitors (MAOBI)). With regard to safety, the risk of developing dyskinesia, motor fluctuations or dystonia among patients with early PD treated with DAs is lower than that among patients treated with levodopa. However, all DAs (ergot and non-ergot) may cause neurological and psychiatric adverse events related to their dopaminergic action. Confusion, impulse control disorders (pathological gambling, hypersexual behaviour, compulsive shopping), daytime sleepiness and hallucinations have been associated with their use, while ergot-derived DAs can, more rarely, induce retroperitoneal, pleural and pericardial fibrosis and cardiac valvulopathy. Cardiac valvular fibrosis and retroperitoneal fibrosis can have severe clinical consequences, and led to withdrawal from the market of lisuride and pergolide. Cabergoline has also been withdrawn in some developed countries. Because of these risks, the clinical use of ergot DAs has been declining. The risk of the above-mentioned non-motor complications is increased among patients taking DAs compared with those given placebo or levodopa alone (8, 9, 14). Treatment tolerability, assessed by discontinuation rates, was better in patients given early levodopa than in patients initiated with DAs, mainly because of side-effects associated with the use of DAs (13). These findings are reported in systematic reviews that considered DAs as a class as well as in those that investigated individual agents or long-acting non-ergot DAs, regardless of the stage of the disease. Systematic reviews of observational studies consistently report that the use of ergot DAs increases the risk of valvular regurgitation, with the effect being dose-dependent (15-17). Non-ergot DAs are more expensive than ergot DAs. All DAs are more expensive than levodopa. In high-income countries the price of DAs varies considerably. Only bromocriptine mesylate 30 x 2.5 mg tab-cap is included in the International Drug Price Indicator Guide. The unit price of bromocriptine ranges from US$ 0.04 in Sudan to US$ 0.30 in South Africa, with a median price of US$ 0.16. In India the annual cost of DAs (mean +/– standard deviation) ranges from US$ 109.4 (+/– US$ 111.9) for the earliest stages of the disease to US$ 128.1 (+/– US$ 144) for advanced stages (18). The Expert Committee noted that several international guidelines deal with the use of DAs in the treatment of PD. Most of them (NICE 2011; SIGN 2010; EFNS 2011) have produced distinct recommendations for use of DAs in early-stage PD and, as an adjunct to levodopa, in advanced-stage PD (10, 19, 20). In early-stage PD, DAs are among the drugs that may be recommended as monotherapy and as a symptomatic treatment, particularly in younger patients. Ergot derivatives are not recommended as first-choice drugs, however, because of the monitoring required in relation to the risk of fibrosis. In advanced-stage PD, DAs are considered as a therapeutic

option for the management of motor complications in patients being treated with levodopa. Decisions regarding the timing of introduction and the type of drug should be made on an individual basis. Non-ergot DAs are the preferred choice. The Committee noted that the availability of antiparkinsonism medicines in primary care is variable, ranging from 12.5% in Africa to 79.1% in Europe (21). The Expert Committee concluded that the most effective treatment for PD is levodopa. Dopamine agonists – like other available treatments for PD – do not modify the course of the disease, and their action is symptomatic. The Expert Committee decided that there was insufficient evidence to show that dopamine agonists offered any clinically relevant efficacy or safety advantages over the existing medicines included in the EML. The Committee therefore recommended that the proposed dopamine agonist medicines should not be added to the EML. References: 1. The selection and use of essential medicines. Report of the WHO Expert Committee, 2013 (including the 18th WHO Model List of Essential Medicines and the 4th WHO Model List of Essential Medicines for Children). Geneva: World Health Organization; 2014. (WHO Technical Report Series, No. 985). 2. Bharucha NE, Bharucha EP, Bharucha AE, Bhise AV, Schoenberg BS. Prevalence of Parkinson's disease in the Parsi community of Bombay, India. Arch Neurol. 1988;45(12):1321-3. 3. de Rijk MC, Launer LJ, Berger K, Breteler MM, Dartigues JF, Baldereschi M, et al. Prevalence of Parkinson's disease in Europe: A collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. Neurology. 2000;54(11 Suppl 5):S21-3. 4. Dotchin C, Msuya O, Kissima J, Massawe J, Mhina A, Moshy A, et al. The prevalence of Parkinson's disease in rural Tanzania. Mov Disord. 2008;23(11):1567-672. 5. Zhang ZX, Roman GC, Hong Z, Wu CB, Qu QM, Huang JB, et al. Parkinson's disease in China: prevalence in Beijing, Xian, and Shanghai. Lancet. 2005;365(9459):595-7. 6. Parkinson's disease: diagnosis and management in primary and secondary care. NICE guidelines [CG35]. London: National Institute for Health and Care Excellence; 2006. Available from: https:// www.nice.org.uk/guidance/cg35. 7. Chondrogiorgi M, Tatsioni A, Reichmann H, Konitsiotis S. Dopamine agonist monotherapy in Parkinson's disease and potential risk factors for dyskinesia: a meta-analysis of levodopacontrolled trials. Eur J Neurol. 2014;21(3):433-40. 8. Stowe RL, Ives NJ, Clarke C, van Hilten J, Ferreira J, Hawker RJ, et al. Dopamine agonist therapy in early Parkinson's disease. Cochrane Database Syst Rev. 2008(2):CD006564. 9. Stowe R, Ives N, Clarke CE, Deane K, Wheatley K, Gray R, et al. Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson s disease patients with motor complications. Cochrane Database Syst Rev. 2010(7):CD007166. 10. Thorlund K, Wu P, Druyts E, Eapen S, Mills EJ. Nonergot dopamine-receptor agonists for treating Parkinson's disease - a network meta-analysis. Neuropsychiatr Dis Treat. 2014;10:767-76. 11. Zhou CQ, Lou JH, Zhang YP, Zhong L, Chen YL, Lu FJ, et al. Long-acting versus standard non-ergot dopamine agonists in Parkinson's disease: a meta-analysis of randomized controlled trials. CNS Neurosci Ther. 2014;20(4):368-76. 12. Zhou CQ, Zhang JW, Wang M, Peng GG. Meta-analysis of the efficacy and safety of long-acting non-ergot dopamine agonists in Parkinson's disease. J Clin Neurosci. 2014;21(7):1094-101. 13. Gray R, Ives N, Rick C, Patel S, Gray A, Jenkinson C, et al. Long-term effectiveness of dopamine agonists and monoamine oxidase B inhibitors compared with levodopa as initial treatment for Parkinson's disease (PD MED): a large, open-label, pragmatic randomised trial. Lancet. 2014;384(9949):1196-205. 14. Kulisevsky J, Pagonabarraga J. Tolerability and safety of ropinirole versus other dopamine agonists and levodopa in the treatment of Parkinson's disease: meta-analysis of randomized controlled trials. Drug Saf. 2010;33(2):147-61. 15. De Vecchis R, Esposito C, Ariano C. Cabergoline use and risk of fibrosis and insufficiency of cardiac valves. Meta-analysis of observational studies. Herz. 2013;38(8):868-80. 16. Rasmussen VG, Ostergaard K, Dupont E, Poulsen SH. The risk of valvular regurgitation in patients with Parkinson's disease treated with dopamine receptor agonists. Mov Disord. 2011;26(5):801-6. 17. Steiger M, Jost W, Grandas F, Van Camp G. Risk of valvular heart disease associated with the use of dopamine agonists in Parkinson's disease: a systematic review. J Neural Transm. 2009;116(2):179-91. 18. Ragothaman M, Govindappa ST, Rattihalli R, Subbakrishna DK, Muthane UB. Direct costs of managing Parkinson's disease in India: concerns in a developing country. Mov Disord. 2006;21(10):1755-8. 19. Diagnosis and pharmacological management of Parkinson's disease: a national clinical guideline. Guideline No. 113. Edinburgh: Scottish Intercollegiate Guideline Network; 2010. Available from: http://www.sign.ac.uk/pdf/sign113.pdf. 20. Oertel WH, Berardelli A, Bloem BR, Bonuccelli U, Burn D, Deuschl G, et al. Early (uncomplicated) Parkinson's disease. In: Giljus NE, Barnes MP, Brainin M, editors. European handbook of neurological management. Volume 1. 2nd ed. Oxford: Blackwell; 2011. 21. Neurological disorders: public health challenges. Geneva: World Health Organization; 2006. Available from: http://www.who.int/mental_health/neurology/neurological_disorders_report_ web.pdf