Donepezil

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

ATC codes: N06DA02

Indication	Dementia due to Alzheimer disease ICD11 code: 6D80
INN	Donepezil
Medicine type	Chemical agent
List type	Core
Formulations	Oral > Liquid: 1 mg per mL (hydrochloride) Oral > Solid > tablet: 5 mg (hydrochloride) ; 10 mg (hydrochloride) ; 5 mg (hydrochloride) (orodispersible) ; 10 mg (hydrochloride) (orodispersible)
EML status history	Application rejected in 2023 (TRS 1049)
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	Donepezil
DrugBank	Donepezil

Expert Committee recommendation

The Expert Committee recognized that Alzheimer disease is a leading cause of disability and dependency worldwide, with high disease burden and associated costs. It also recognized that there is a substantial demand and need for effective treatments for dementia due to Alzheimer disease. The Committee noted that medicines such as donepezil and other cholinesterase inhibitors have been available in several regions of the world for symptomatic management of dementia due to Alzheimer disease for a long time but they had not previously been evaluated for inclusion on the EML. The Committed acknowledged that moderate-certainty evidence suggested donepezil may be associated with a statistically significant effect on cognitive outcome scores compared with placebo. However, most of the Committee members considered that these improvements were unlikely to be clinically meaningful. Committee members held different views about the interpretation of the clinical importance of possible benefits associated with donepezil. Most of them considered the benefits of donepezil at the population level to be minimal or nil. A few members considered the benefits to be small but would consider offering donepezil to people with dementia due to Alzheimer disease in the absence of other effective treatments. All experts agreed that there was no clear evidence of prolonged benefits over time. The Committee noted from the evidence that the effect of donepezil on activities of daily living was limited, while no difference on behavioural symptoms and quality of life was found. The limited duration of studies was also considered by the Committee to be inadequate to assess the longer-term clinical benefit of a treatment for a chronic degenerative disorder such as Alzheimer disease. There is no evidence that donepezil or other cholinesterase inhibitors can reverse or slow the progression of Alzheimer disease. The Committee accepted that the adverse effects of donepezil are generally mild and that donepezil is well tolerated in most patients. However, the Committee noted that the risk of adverse effects increases with higher doses, and there is potential for numerous drug–drug and drug–disease interactions, especially considering that polypharmacy is common in older people. The Committee

considered that patients included in dementia trials are generally younger and characterized by a better performance status compared with patients seen in routine dementia health care facilities, which affects generalizability of trial results to the population with Alzheimer dementia encountered in routine clinical care. Overall, it was the view of most of the Committee members that the overall benefit-to-harm profile of donepezil was unfavourable. The Committee noted evidence from studies conducted primarily in high-income countries that determined donepezil to be cost-effective compared with placebo when added to standard of care for patients with dementia. However, given the Committee's views about the benefit-to-harm profile, this evidence was not considered compelling and did not influence the recommendation. The Committee noted that diagnosis of Alzheimer disease dementia in later stages is potentially feasible even in the context of resource-constrained settings, as it is mostly based on clinical symptoms, which become clearer as the disease progresses. However, diagnosis in early stages is more challenging, and it is usually managed by specialized health care professionals experienced in the use of validated memory or cognitive function tests. The Committee expressed concerns about the feasibility and availability of specialized diagnostic services for Alzheimer disease, especially in resource-constrained settings. While the 2015 WHO guidelines state that donepezil may be offered in non-specialist settings, clinicians must be adequately trained to ensure safe and effective treatment, which may be an important barrier to diagnosis and feasibility of appropriate use. The Committee noted that donepezil is already included in some national essential medicines and reimbursement lists. The Committee also noted however that debate over the overall clinical benefit at the population level in recent years has resulted in reconsideration of continued reimbursement for donepezil in some countries, notably France. Other countries have introduced prescribing limitations or shared-care protocols and monitoring in specialist settings. Therefore, based on these considerations, the Expert Committee did not recommend inclusion of donepezil on the EML for the treatment of dementia due to Alzheimer disease.

Background

Medicines for Alzheimer disease dementia have not previously been evaluated for inclusion in the EML.

Public health relevance

In 2019, it was estimated that there were over 55 million people with dementia worldwide, 61% of whom lived in low- and middle-income countries. Due to rapidly ageing populations, this number is set to increase to 78 million by 2030 and to at least 139 million by 2050. Dementia causes disability and care dependency in older age and ranks as the 25th leading cause of disability-adjusted life years. Alzheimer disease and other dementias were the seventh leading cause of death globally in 2019 (1).

Benefits

Consensus is lacking on what represents clinically important effect sizes for outcome measures for patients with Alzheimer disease dementia, their families or care-givers or their doctors (2–4). The application identified national health technology appraisals undertaken to inform dementia clinical guideline development, and additional systematic reviews and randomized trials. The application presented a brief summary of findings of the 2018 United Kingdom National Institute for Health and Care Excellence (NICE) dementia care health technology appraisal of cholinesterase inhibitors (donepezil, galantamine, rivastigmine) and memantine for treatment of Alzheimer disease (5). This appraisal updated the 2016 NICE clinical guidelines and included data from 19 randomized trials comparing donepezil with placebo in adults with a diagnosis of mild to moderately severe Alzheimer disease (6). Pooled cognitive outcomes showed a statistically significant difference in favour of donepezil measured using cognitive assessment scale scores: • Mini Mental State Examination score: weighted mean difference (WMD) 1.17 points (95% confidence interval (CI) 0.88 to 1.45) at 12 weeks and 1.21 points (95% CI 0.84 to 1.57) at 24 weeks; • Alzheimer Disease Assessment Scale–Cognitive Subscale score: WMD −1.97 (95% CI −3.38 to −0.56) at 12 weeks and −2.90 (95% CI −3.61 to −2.18) at 24 weeks. A 2018 systematic review and network meta-analysis of 142 studies (110 randomized controlled trials, 21 non-randomized controlled trials and 11 cohort studies) evaluated the comparative effectiveness and safety of cholinesterase inhibitors or memantine for Alzheimer disease (7). The network meta-analyses of cognitive outcomes measured using Mini Mental State Examination scale (56 randomized controlled trials, eight treatments, 10 446 participants) found the following interventions to be superior to placebo: • donepezil (mean difference (MD) 1.39, 95% credible interval (CrI) 0.53 to 2.24), • donepezil + memantine (MD 2.59, 95% CrI 0.12 to 4.98), • transdermal rivastigmine (MD 2.02, 95% CrI 0.02 to 4.08). Network meta-analyses of cognitive outcomes measured using the Alzheimer Disease Assessment Scale–Cognitive Subscale (53 randomized controlled trials, six treatments, 11 348 participants) found the following interventions to be superior to placebo: • donepezil (MD −3.29, 95% CrI –

4.57 to –1.99), • galantamine (MD –2.13, 95% CrI –3.91 to –0.27). A subsequent systematic review and individual patient data network meta-analysis of 80 randomized controlled trials (21 138 participants) including 12 randomized controlled trials with individual patient data (6906 participants) evaluated the comparative efficacy and safety of cholinesterase inhibitors or memantine by patient characteristics for managing Alzheimer dementia (8). Significant improvements in Mini Mental State Examination scores were seen for donepezil (MD 1.41, 95% CI 0.51 to 2.32) and donepezil + memantine (MD 2.57, 95% CI 0.07 to 5.07) compared with placebo. Transdermal rivastigmine and the combinations of donepezil + memantine, galantamine + memantine, and transdermal rivastigmine + memantine showed MDs greater than 1.40, however associated 95% CIs were wide and included zero. Donepezil, memantine and their combination showed a larger improvement in cognitive performance in patients with moderate-to-severe cognitive impairment. Donepezil and transdermal rivastigmine showed the greatest improvement in cognitive performance in patients with mild-to-moderate disease. A 2019 meta-analysis of 36 randomized trials (6611 participants) evaluated the efficacy and safety of cholinesterase inhibitors and memantine for the treatment of Alzheimer disease (9). From studies of donepezil versus placebo, there were significant differences favouring donepezil in cognition as measured using the Alzheimer Disease Assessment Scale–Cognitive Subscale, functional outcomes measured using the AD Cooperative Study Activities of Daily Living subscale and global assessment of change measured using Clinician's Interview-Based Impression of Change Plus Caregiver Input scale. No effect of donepezil was observed for behavioural outcomes measured using the Neuropsychiatric Inventory scale.

Harms

The application described donepezil as being generally safe and well tolerated, with minor side-effects including nausea, vomiting, diarrhoea, loss of appetite, weight loss, muscle cramps and urinary difficulties. QTc interval prolongation and torsade de pointes have been reported in postmarketing studies and routine pulse checks are recommended at baseline, monthly intervals during dose titration, and 6-monthly intervals thereafter (10). Rhabdomyolysis and neuroleptic malignant syndrome have been reported rarely in association with donepezil. Safety outcomes from the systematic reviews and meta-analyses described above were not reported in the application but are summarized below. The 2018 systematic review reported no increased risk of adverse events, falls or bradycardia with any of the medicines evaluated. Increased risks of diarrhoea, nausea and vomiting were reported for donepezil (7). In the systematic review and individual patient data network meta-analysis, a network meta-analysis of studies with individual patient data and aggregate data, compared all available treatments for adverse events (8). According to P-scores (a statistical score used to rank treatments in meta-analyses), oral rivastigmine and donepezil had the least favourable safety profiles. Estimated treatment effects were imprecise compared with placebo. The 2019 meta-analysis noted that high drop-out rates and adverse effects associated drop-outs were observed in randomized controlled trials of cholinesterase inhibitors and memantine. The meta-analysis reported discontinuation due to adverse events and drop-outs due to any reason. Compared with placebo, donepezil was significantly associated with increased discontinuation due to adverse events (odds ratio (OR) 1.24, 95% CI 1.04 to 1.19). There was no significant difference between donepezil and placebo for drop-outs due to any reason (OR 1.12, 95% CI 0.91 to 1.37) (9). Adverse effects observed were gastrointestinal and nervous system effects including nausea, vomiting, diarrhoea, anorexia, dizziness, depression and headache; however, the incidence of these effects was not compared.

Additional evidence

Additional evidence A Cochrane systematic review of 30 randomized controlled trials (8257 participants) identified during the application review process assessed the efficacy and safety of donepezil in people with Alzheimer disease of all severities, and also compared efficacy and safety of different doses of donepezil (11). Most of the included studies were of 6 months' duration or shorter. One study (286 participants) had a duration of 52 weeks. The studies tested mainly donepezil capsules at a dose of 5 mg/day or 10 mg/day. Two studies tested a slow-release oral formulation that delivered 23 mg/day. Most of the included studies (n=21) included participants with mild-to-moderate disease. The primary analysis compared the efficacy and safety of donepezil 10 mg/day versus placebo at 24 to 26 weeks of treatment (13 randomized controlled trials, 3396 participants). Seventeen studies were industry funded or sponsored, four studies were funded independently of industry and for nine studies no information was given on the funding source. Donepezil was associated with improved outcomes after 26 weeks for cognitive function measured with the Alzheimer Disease Assessment Scale–Cognitive Subscale (MD –2.67, 95% CI –3.31 to –2.02), Mini Mental State Examination score (MD 1.05, 95% CI 0.73 to 1.37) and the Severe Impairment Battery (MD 5.92, 95% CI 4.53 to 7.31). Donepezil was also associated with improved functioning measured with the Alzheimer Disease Cooperative Study activities of daily living score for severe Alzheimer disease (MD 1.03, 95% CI 0.21 to 1.85). A higher proportion of participants treated with donepezil

experienced improvement on the Clinician-rated Global Impression of Change scale (OR 1.92, 95% CI 1.54 to 2.39). No difference was observed between treatment groups for behavioural symptoms measured by the Neuropsychiatric Inventory (MD –1.62, 95% CI –3.43 to 0.19) or by the Behavioural Pathology in Alzheimer Disease scale (MD 0.4, 95% CI –1.28 to 2.08). No difference was observed between treatment groups for quality of life (MD –2.79, 95% CI –8.15 to 2.56). Participants treated with donepezil were more likely to withdraw from the studies before the end of treatment (24% versus 20%; OR 1.25, 95% CI 1.05 to 1.50) or to experience an adverse event during the studies (72% versus 65%; OR 1.59, 95% 1.31 to 1.95).

Cost / cost effectiveness

The application presented the findings of multiple systematic reviews, health technology assessments and other studies that evaluated the cost–effectiveness of treatments for Alzheimer disease, including donepezil. Most were conducted more than 15 years ago, before the introduction of generic donepezil, and may be of limited applicability today because of changes in acquisition costs. The most recent systematic review of seven cost–effectiveness analyses was published in 2012 (14). Analyses for patients treated in trials of donepezil versus placebo showed incremental cost–effectiveness ratios ranging from dominance (clinically superior and cost saving) up to €20 867 per quality-adjusted life year (QALY), suggesting that donepezil was a cost-effective or even a cost-saving strategy at common willingness to pay thresholds in high-income countries. A 2020 analysis of the cost–effectiveness of treatments for Alzheimer disease using real-world evidence from Thailand utilized a simulation model to compare the costs and cost–effectiveness of donepezil, galantamine, rivastigmine, memantine and no treatment (15). Effectiveness was measured as QALYs, and costs included direct medical expenditures (outpatient, inpatient and emergency visits; medications), out-of-pocket payments, costs of transportation and formal caregiving services, and the indirect costs of unpaid informal caregiving time. From a societal perspective, the mean incremental cost–effectiveness ratio for donepezil treatment was US$ 4062 per QALY, and thus cost-effective at the willingness-to-pay threshold of 160 000 Thai bahts/QALY gained (US$ 4994/QALY gained) applied in Thailand. The incremental cost–effectiveness ratio decreased with early introduction of treatment. Multiple other (older) economic evaluation studies, primarily conducted in high-income settings, have found donepezil to be a cost-effective intervention compared with placebo (16–28). A global survey conducted by the applicants collected information on the price of a 5 mg tablet of donepezil. Reported prices ranged from US$ 0.13 to US$ 6.60 per tablet.

WHO guidelines

The 2015 WHO Mental Health Gap Action Programme (mhGAP) guidelines make the following recommendations on cholinesterase inhibitors and memantine for the treatment of dementia in non-specialist health settings (12). “Cholinesterase inhibitors and memantine may be offered to people with dementia in non-specialist health settings. Non-specialists need to be trained and supervised to ensure competence in diagnosis and monitoring. The use of cholinesterase inhibitors should be focused upon those with mild to moderate Alzheimer’s disease, where the majority of evidence is available. Memantine may be considered for those with moderate to severe Alzheimer’s disease and vascular dementia. Memantine should not be prescribed for Lewy Body dementia.” (quality of evidence: very low, strength of recommendation: conditional). “Rationale: Cholinesterase inhibitors and memantine offer symptomatic benefits in cognitive, functional, global and behavioural outcomes, although the size of this benefit is uncertain and the quality of the evidence very low. Adverse effects and safety in the long-term may represent serious concerns. Dementia diagnosis and subtype definition and management with the above medications require training, supervision, and support. Moreover, these medications are associated with high acquisition costs. Remarks: Consideration should be given to adherence and monitoring of adverse effects.” The 2016 WHO mhGAP Intervention Guide includes the following recommendations for the use of cholinesterase inhibitors or memantine in dementia (13). “For dementia without behavioural and/or psychological symptoms, do not consider cholinesterase inhibitors (like donepezil, galantamine and rivastigmine) or memantine routinely for all cases of dementia. Consider medications only in settings where specific diagnosis of Alzheimer disease can be made AND where adequate support and supervision by specialists and monitoring (for side-effects and response) from carers is available. If appropriate: For dementia with suspected Alzheimer disease, and with close monitoring, consider cholinesterase inhibitors (e.g. donepezil, galantamine, rivastigmine) OR memantine. For dementia with associated vascular disease, consider memantine.”

Availability

Donepezil is available in innovator and generic brands. Medicines to treat dementia are approved in fewer low- and middle-income countries compared with high-income countries (78% and 97%, respectively). Generics are reported to be available in 59% of low-

and middle-income countries compared with 85% of high-income countries. Full reimbursement of such medicines has been reported in 26% of low- and middle-income compared to 76% of high-income countries (1).

1. Global status report on the public health response to dementia. Geneva: World Health Organization; 2021 (https://apps.who.int/iris/handle/10665/344701, accessed 6 October 2023).
2. Molnar FJ, Man-Son-Hing M, Fergusson D. Systematic review of measures of clinical significance employed in randomized controlled trials of drugs for dementia. J Am Geriatr Soc. 2009;57(3):536–46.
3. Blanco-Silvente L, Castells X, Garre-Olmo J, Vilalta-Franch J, Saez M, Barceló MA, et al. Study of the strength of the evidence and the redundancy of the research on pharmacological treatment for Alzheimer's disease: a cumulative meta-analysis and trial sequential analysis. Eur J Clin Pharmacol. 2019;75(12):1659–67.
4. Burback D, Molnar FJ, St John P, Man-Son-Hing M. Key methodological features of randomized controlled trials of Alzheimer's disease therapy. Minimal clinically important difference, sample size and trial duration. Dement Geriatr Cogn Disord. 1999;10(6):534–40.
5. Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease. London: National Institute for Health and Care Excellence; 2018 (Technology appraisal guidance TA217) (https://www.nice.org.uk/guidance/ta217, accessed 6 October 2023).
6. Bond M, Rogers G, Peters J, Anderson R, Hoyle M, Miners A, et al. The effectiveness and cost-effectiveness of donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (review of Technology Appraisal No. 111): a systematic review and economic model. Health Technol Assess. 2012;16(21):1–470.
7. Tricco AC, Ashoor HM, Soobiah C, Rios P, Veroniki AA, Hamid JS, et al. Comparative effectiveness and safety of cognitive enhancers for treating Alzheimer's disease: systematic review and network metaanalysis. J Am Geriatr Soc. 2018;66(1):170–8.
8. Veroniki AA, Ashoor HM, Rios P, Seitidis G, Stewart L, Clarke M, et al. Comparative safety and efficacy of cognitive enhancers for Alzheimer's dementia: a systematic review with individual patient data network meta-analysis. BMJ Open. 2022;12(4):e053012.
9. Li DD, Zhang YH, Zhang W, Zhao P. Meta-analysis of randomized controlled trials on the efficacy and safety of donepezil, galantamine, rivastigmine, and memantine for the treatment of Alzheimer's disease. Front Neurosci. 2019;13:472.
10. Rowland JP, Rigby J, Harper AC, Rowland R. Cardiovascular monitoring with acetylcholinesterase inhibitors: a clinical protocol. Adv Psychiatr Treat. 2007;13(3):178–84.
11. Birks JS, Harvey RJ. Donepezil for dementia due to Alzheimer's disease. Cochrane Database Syst Rev. 2018;6(6):CD001190.
12. Update of the Mental Health Gap Action Programe (mhGAP) guideline for mental, neurological and substance use disorders. May 2015. Geneva: World Health Organization; 2015 (https://apps.who.int/iris/handle/10665/204132, accessed 6 October 2023).
13. mhGAP intervention guide for mental, neurological and substance use disorders in nonspecialized health settings: mental health Gap Action Programme (mhGAP) – version 2.0. Geneva: World Health Organization; 2016 (https://apps.who.int/iris/handle/10665/250239, accessed 6 October 2023).
14. Pouryamout L, Dams J, Wasem J, Dodel R, Neumann A. Economic evaluation of treatment options in patients with Alzheimer's disease: a systematic review of cost-effectiveness analyses. Drugs. 2012;72(6):789–802.
15. Kongpakwattana K, Chaiyakunapruk N. Application of discrete-event simulation in health technology assessment: a cost-effectiveness analysis of Alzheimer's disease treatment using real-world evidence in Thailand. Value Health. 2020;23(6):710–8.
16. Knapp M, Kin gD, Romeo R, Adams J, Baldwin A, Ballard C, et al. Cost-effectiveness of donepezil and memantine in moderate to severe Alzheimer's disease (the DOMINO-AD trial). Int J Psychiatry. 2016;32(12):1205–16.
17. da Silva LR, Vianna CMM, Mosegui GBG, Peregrino AAF, Marinho V, Laks J. Cost-effectiveness analysis of the treatment of mild and moderate Alzheimer's disease in Brazil. Braz J Psychiatry. 2019;41(3):218–24.
18. Hartz S, Getsios D, Tao S, Blume S, Maclaine GD. Evaluating the cost effectiveness of donepezil in the treatment of Alzheimer's disease in Germany using discrete event simulation. BMC Neurol. 2012;12(1):2.
19. Teipel SJ, Ewers M, Reisig V, Schweikert B, Hampel H, Happich M. Long-term cost-effectiveness of donepezil for the treatment of Alzheimer's disease. Eur Arch Psychiatry Clin Neurosci. 2007;257(6):330–6.
20. López-Bastida J, Hart W, García-Pérez L, Linertová R. Cost-effectiveness of donepezil in the treatment of mild or moderate Alzheimer's disease. J Alzheimers Dis. 2009;16(2):399–407.
21. Fuh JL, Wang SJ. Cost-effectiveness analysis of donepezil for mild to moderate Alzheimer's disease in Taiwan. Int J Psychiatry. 2008;23(1):73–8.
22. Feldman H, Gauthier S, Hecker J, Vellas B, Hux M, Xu Y, et al. Economic evaluation of donepezil in moderate to severe Alzheimer disease. Neurology. 2004;24(63):644–50.
23. Wimo A, Winblad B, Engedal K, Soininen H, Verhey F, Waldemar G, et al. An economic evaluation of donepezil in mild to moderate Alzheimer's disease: results of a 1-year, double-blind, randomized trial. Dement Geriatr Cogn Disord. 2003;15(1):44–54.
24. Jönsson L, Lindgren P, Wimo A, Jönsson B, Winblad B. The cost-effectiveness of donepezil therapy in Swedish patients with Alzheimer's disease: a Markov model. Clin Ther. 1999;21(7):1230–40.
25. O'Brien BJ, Goeree R, Hux M, Iskedjian M, Blackhouse G, Gagnon M, et al. Economic evaluation of donepezil for the treatment of Alzheimer's disease in Canada. J Am Geriatr Soc. 1999;47(5):570–8.
26. Getsios D, Blume S, Ishak KJ, Maclaine GD. Cost effectiveness of donepezil in the treatment of mild to moderate Alzheimer's disease: a UK evaluation using discrete-event simulation. Pharmacoeconomics. 2010;28(5):411–27.
27. Neumann PJ, Hermann RC, Kuntz KM, Araki SS, Duff SB, Leon J, et al. Cost-effectiveness of donepezil in the treatment of mild or moderate Alzheimer's disease. Neurology. 1999;52(6):1138–45.
28. Small GW, Donohue JA, Brooks RL. An economic evaluation of donepezil in the treatment of Alzheimer's disease. Clin Ther. 1998;20(4):838–50.