A.14	Donepezil – Alzheimer disease – EML
Draft recommendation	☐ Recommended ☒ Not recommended Justification: It is impressive to recognize the importance of the WHO EML in the perception of the letters of support, and likewise, throughout the application. With great influence comes necessity to be objective in relation to meaningful effectiveness and safety. The WHO-EML is recognized as influential because of the rigour in selecting essential medicines – only those that are effective, safe and affordable either by systems or users, or both, may be listed. The list is powered by health need, effectiveness, and safety, and not by demand. Studies found moderate- to high-certainty evidence that donepezil 5 mg and donepezil 10 mg, have a slight beneficial effect on cognition, although the size of the change is unlikely to be clinically important. Donepezil 10 mg is probably associated with more adverse events than placebo. The data suggest that donepezil 10 mg has the greatest effect on cognition, but at the cost of adverse effects. The beneficial effect is modest. There is no effect on QoL, and there is not enough evidence that these drugs have meaningful disease modifying activity. Diagnostic and post diagnostic services in AD and for treatment follow-up both may constitute a limitation, especially in low-resource settings. A WHO 2015 guideline recommendation stressed that AChE-I could be offered to patients in in non-specialist health settings but the non-specialists had to be trained and supervised in diagnosis and monitoring. However, for this there was low quality of evidence and a conditional recommendation, which does not bind EML inclusion, in my view. Despite the increase in the number of cases and the associated costs, **there is still no effective treatment to reverse or slow the progression of AD.** Although there is evidence for a slight beneficial effect with donepezil in comparison with placebo, the inclusion in the WHO-EML responds far more to a societal demand than to a definite evidence of benefit. The former aspect might be a relevant argument *per se*, a.k.a. the letters of support, the magnitude of incidence and prevalence of dementia worldwide, and the burden to health systems and society. I do not underestimate this argument. However, I do not find the evidence compelling enough to recommend inclusion in the EML.

Does the proposed medicine address a relevant public health need?	☒ Yes ☐ No ☐ Not applicable Comments: Dementia is a huge health issue worldwide, with an estimate of approximately 35.6 million people, with 7.7 million diagnoses each year[1]. Of these, 61 % live in low or middle-income countries. Dementia is a leading cause of disability and dependency and the 7th leading cause of death globally. Alzheimer´s disease is the leading cause of dementia, accounts for 60–75% of all cases[1]. An overview of prevalence in specific countries [India (6 million), Mexico (1.3 million), UK (900,000), Brazil (2 million), Indonesia (1.2 million in 2015 projecting 4 million by 2030)] leaves no doubt as to the importance of this disease and its burden to society. Dementia is diagnosed when cognitive or behavioral (neuropsychiatric) symptoms (a) interfere with work and day-to-day abilities, (b) represent a decline in previous levels of cognitive functioning and performance, and (c) are not explained by *delirium* or major psychiatric condition. Differential diagnosis of Alzheimer´s is only definitive at autopsy (presence of senile plaques (SP), neurofibrillary tangles, and neuronal and synaptic loss)[1]. According to Birks and Harvey "The diagnostic criteria for the clinical diagnosis of Alzheimer's disease (NINCDS-ADRDA) require formal mental status testing, a medical history, physical neurological and psychiatric examination, laboratory tests and a scan"[2]. To give support to the application, letters from NGOs in Madagascar, France, India, UK, Mexico, Brazil, Kenya, Indonesia, Oman, and the US basically reiterated the importance of dementia as a public health issue and stressed that adding dementia drugs to the EML would result in better access, provision or reimbursement of these drugs in their individual countries. The general understanding is that not being part of the WHO EML will impede reimbursement and be detrimental to equitable access to evidence-based care. One of the letters states "Having dementia drugs on the EML will help ensure there will be drugs available, in adequate amounts, at the appropriate dosage forms with assured quality and at prices individuals and the community can afford" – perhaps this also implies prequalified drugs and an expanded market, which is a sound assumption. The letters of support also state that a result of not having dementia drugs approved in the WHO EML is the use of anti-psychotics as treatment. I am not sure whether inclusion on the EML as mandatory for access is a reality in most countries. The WHO-EML is indeed a list which all countries can resort to in terms of best (effective and safe) and affordable treatment options and may inform country health systems but may not directly intervene in country drug adoption, which is subject to other considerations. The application also brings forth the information that currently 28 countries include donepezil in their national EML (WHO Global EML Database at https://global.essentialmeds.org/dashboard/countries). This in fact implies that presence in the WHO-EML is not a strict requirement if countries find the will and means or make the decision to include donepezil in their country lists. Country-wise drug selection or incorporation is not mentioned in each letter. For example, in Brazil dementia drugs are on the National EML.

Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication? (this may be evidence included in the application, and/or additional evidence identified during the review process)	☒ Yes ☐ No ☐ Not applicable Comments: Despite the increase in the number of cases and the associated costs, **there is still no effective treatment to reverse or slow the progression of AD**[1]. Donepezil is a piperidine-derived cholinergic drug, a non-competitive acetylcholinesterase inhibitor (AChE-I), approved in 1996, for the therapeutic management of mild to moderate cases of AD. It also acts as also acts at the molecular and cellular level in the pathogenesis of AD (inhibition of various aspects of glutamate-induced excitotoxicity, reduction of early expression of inflammatory cytokines, induction of a neuroprotective isoform of AChE, and reduction of oxidative stress-induced effects). The medicines is to be taken daily, in the evening. None of the dosage regimens with donepezil (from 5 to 23mg/day) have been able to interrupt the progression of AD. Nevertheless, the drug is characterized by good patient tolerance and mild adverse effects[1]. Several SR and MA describing and measuring effects of donepezil in AD exist, most comparing to placebo. Battle et al (2021): eight trials (4373 participants). For cognition, the results showed that donepezil 5 mg improves cognition slightly, although size of the effect is unlikely to be clinically important (mean difference (MD) −0.92 Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) points (range 0 to 70), 95% confidence interval (CI) −1.44 to −0.40; high-certainty evidence). Donepezil 10 mg (MD −2.21 ADAS-Cog points, 95% CI −3.07 to −1.35; moderate-certainty evidence) probably also improve cognition, although the larger effect estimates still may not be clinically important[3]. Veroniki et al (2022): 80 randomized controlled trials (RCTs) including 21,138 adults with AD, and 12 RCTs with IPD including 6906 patients. Donepezil (mean difference (MD)=1.41, 95% CI: 0.51 to 2.32) improved MMSE score (56 RCTs, 11,619 participants; CINeMA score: moderate) compared with placebo[4]. Guo et al (2020): 936 records screened, 54 trials included. For cognition, combination therapy (memantine + donepezil) was better than donepezil monotherapy (MD 4.70, 95% CI 0.68 to 8.75), and placebo showed the worst effect. For daily activities and neuropsychiatric symptoms donepezil fared closer to placebo[5]. Knorz and Quante (2022) found better results for donepezil when in combination therapy with other AD drugs, herbal medicines and drugs for other indications[6]. Birks and Harvey (2018) authors a Cochrane review exclusively aimed at donepezil (to assess the effectiveness and safety in people with mild, moderate or severe AD; to compare effectiveness and safety of different doses; and to assess the effects on healthcare resource use and costs) and no updated versions have been published since. Thirty studies involving 8257 participants for the review, of which 28 studies reported detail for the meta-analyses. Most studies were 6 months or less. There is moderate-quality evidence that people with mild, moderate or severe AD, treated for 12 or 24 weeks experience small benefits in cognitive function, activities of daily living and clinician-rated global clinical state. Benefits on 23 mg/day (slow-release dosage form) were no greater than on 10 mg/day, and benefits on the 10 mg/day dose were marginally larger than 5 mg/day. Almost all evidence was of moderate quality, downgraded due to study limitations[2]. Marucci et al (2021): There is evidence indicating that donepezil at dosages of 5 and 10 mg/day improves cognition and global clinical function in the short term (up to 24 weeks) and long term (for up to about 1 year) in patients with mild to moderate AD. However, since AD is characterized by longtime evolution, a limit is in the relatively short time of observation. No effect of donepezil on Quality of Life (QoL) was demonstrated in clinical studies. Overall, the benefits of the AChE-Is on cognition are modest and there is not enough evidence that these drugs have a clinically meaningful disease modifying activity[7]. There are guidelines from HTA agencies that support effectiveness of donepezil in mild to moderate AD.

Does adequate evidence exist for the safety/harms associated with the proposed medicine? (this may be evidence included in the application, and/or additional evidence identified during the review process)	☒ Yes ☐ No ☐ Not applicable Comments: Battle et al (2021): The results showed that there was probably little to no difference between donepezil 5 mg and placebo in the number of adverse events (odds ratio (OR) 1.22, 95% CI 0.94 to 1.58; moderate-certainty evidence), but there were slightly more adverse events with donepezil 10 mg than with placebo (OR 1.95, 95% CI 1.20 to 3.15; high-certainty evidence)[3]. Veroniki et al (2022): According to P-score, donepezil had the second least favorable safety profile regarding AE (OR=1.08, 95%CI: 0.87 to 1.35, P-score=30%), but in these comparisons the odds of experiencing an AE were imprecise and not importantly different from placebo[4]. Guo et al (2020): Adverse events were similar across the 54 included trials[5]. Birks and Harvey (2018): Participants receiving 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, 2846 participants, 12 studies) or to experience an adverse event during the studies (72% vs 65%, OR 1.59, 95% 1.31 to 1.95, 2500 participants, 10 studies). Rates of withdrawal and of adverse events before end of treatment were higher the higher the dose. Almost all evidence was of moderate quality, downgraded due to study limitations[2].
Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable Comments: Donepezil has a 100% bioavailability, reaches a plasma peak in 3–4 h, is metabolized by hepatic P-450 enzymes (CYP2D6, CYP3A4) and has a half-life of about 60–90 h. Its long half permits administration of the drug once daily[7]. Usually well tolerated. However, several adverse effects may be of concern, especially in higher doses. A rare occurrence is Neuroleptic Malignant Syndrome (NMS), characterised by hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated serum creatine phosphokinase levels; additional signs may include myoglobinuria (rhabdomyolysis) and acute renal failure. Other serious events are cardiac, such as QTc interval prolongation and Torsade de Pointes Usual adverse effects of donepezil are insomnia, nausea, vomiting, diarrhoea, loss of appetite, muscular cramps, dyspepsia, headaches, sleepiness, dizziness, depression, weight loss, abnormal dreams, augmented urinary frequency, loss of consciousness, bradycardia, hypertension, arthritis, skin discoloration.

Are there any special requirements for the safe, effective and appropriate use of the medicines? (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	☒ Yes ☐ No ☐ Not applicable Comments: Patients with a suspicion of AD should be referred to a specialized service in neurology, gerontology, or psychiatry or to a specialized physician (in dementia assessment) for diagnosis and follow-up. According to Birks and Harvey "The diagnostic criteria for the clinical diagnosis of Alzheimer's disease (NINCDS-ADRDA) require formal mental status testing, a medical history, physical neurological and psychiatric examination, laboratory tests and a scan"[2]. Hepatic function must be monitored. Cardiac follow-up (ECG), routine pulse checks, and monitoring of gastrointestinal problems (such as ulcers). Monitoring for signs of rhabdomyolysis is desired. According to a 2015 WHO guideline, the medicine may be offered in non-specialist health settings. Non-specialists need to be trained and supervised to ensure competence in diagnosis and monitoring.
Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings?	☒ Yes ☐ No ☐ Not applicable Comments: Guo et al (2020): Costs involved both the direct costs of treatment and caregivers and the indirect costs, such as inability to work. For cost alone, donepezil was the fourth in line (less costly that placebo, combination with memantine and costlier that memantine alone). When considering effectiveness and cost, combination therapy, memantine and donepezil showed no differences in cognition, daily activities and QoL[4]. Birks and Harvey (2018): There was no evidence of a difference between donepezil and placebo for patient total healthcare resource utilisation (there is some evidence that use of donepezil is neither more nor less expensive compared with placebo when assessing total healthcare resource costs). Donepezil, in comparison to placebo, was considered almost neutral in terms of cost[6]. The available evidence regarding costs comes almost entirely from high-income countries. Price ranged from a low 0.13 – 6.6 USD for a tablet. There is a 2012 study referred as cost-effectiveness analysis, in which the medicine is considered more cost-effective than placebo[8]. Other more recent studies have also found the drug more cost-effective than placebo (Thailand, Brazil, UK, Germany, Taiwan, Canada, France, Australia, Sweden, Denmark, Finland, Netherlands, Norway, USA).

Are there any issues regarding the registration of the medicine by national regulatory authorities? (e.g. accelerated approval, lack of regulatory approval, off-label indication)	☒ Yes ☐ No ☐ Not applicable Comments: The application requires 5mg and 10mg tablets, 5mg and 10mg orodispersible tablet and 1mg/1mL oral solution. Donepezil has been approved for use in many countries and health regulatory agencies including the United States FDA, the European Medicines Agency (EMA), the United Kingdom Medicines and Healthcare products Regulatory Agency (UK MHRA) among others. Tablets are more commonly registered. The drug is not on-patent. It is licensed in 38 countries[7].
Is the proposed medicine recommended for use in a current WHO guideline? (refer to: https://www.who.int/publications/who-guidelines)	☒ Yes ☐ No ☐ Not applicable Comments: Donepezil is recommended for use in dementia care in the 2015 WHO Mental Health Gap Action Programme (mhGAP) guidelines for mental, neurological and substance use disorders (accessed at https://apps.who.int/iris/handle/10665/204132). The recommendation reads as follows: "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. Quality of Evidence: Very low Strength of recommendation: Conditional"

Additional References

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