A.14	Donepezil – Alzheimer disease – EML
Draft recommendation	☐ Recommended ☒ Not recommended Justification: This application relates to the inclusion on the WHO Model list of donepezil as an individual medicine. The link between the neurotransmitter acetylcholine and memory was known since the 70s. The "cholinergic hypothesis of Alzheimer's disease" was based on neuropathological and clinical pharmacological arguments that increasing cholinergic activity by pharmacological means would improve symptoms. The approach was similar to the improvement observed on the motor deficits of people with Parkinson disease after the normalisation of dopaminergic transmission using levodopa. Agents blocking the enzyme acetylcholinesterase, responsible for the degradation of acetylcholine, are licensed since the 90s in more than 60 countries for the treatment of mild-to-advanced stages of Alzheimer's disease. These are donepezil, rivastigmine, and galantamine. Their therapeutic effects are comparable. All have demonstrated statistically significant symptomatic benefits on cognition in short-term, double-blind placebo-controlled randomised clinical trials (RCTs). However, their benefit/risk ratio and magnitude of clinical value are still being debated. The difference between active treatment and placebo is about three points on the cognitive section of the Alzheimer's disease assessment scale (ADAS-Cog, scored out of 70) over six months. This equates approximately to the decline expected over the same period. The negligible overall clinical benefits at a population level explains why some countries, notably France, have removed from the list of available reimbursed drugs by the public health sector or other countries introduced limitations or shared-care protocol and monitoring in specialist settings. The debate around reliable measures combining clinician and caregiver assessment and functional outcomes, as well as thresholds for a clinically important difference in cognition scores that matter to people with Alzheimer's disease and their families has been intense, but no consensus has been achieved so far. This Reviewer understands that some people affected by Alzheimer's disease may benefit from the use of donepezil and other anticholinergic medications. However, based on the major concern about the actual clinical value at the population level, would not recommend donepezil to be included to the WHO Model List of Essential Medicines. The lack of clinical innovation in the treatment of Alzheimer's disease should not be a reason for the inclusion of treatment options regardless of their clinical value.

Does the proposed medicine address a relevant public health need?	☒ Yes ☐ No ☐ Not applicable Comments: Alzheimer's disease is the most common cause of dementia. The WHO estimates that more than 139 million individuals globally will have dementia by 2050 and has recognized dementia as a global public health crisis. Dementia is also a leading cause of disability and dependency, with high global costs currently estimated at 1.3 trillion USD and expected to rise to 2.8 trillion USD by 2030. While the number of people with dementia is rising, in some high-income countries such as USA, UK, and France, age-specific incidence rates are lower in more recent cohorts compared with cohorts from previous decades collected using similar methods and target populations. In contrast, age-specific dementia prevalence in Japan, South Korea, Hong Kong, and Taiwan looks as if it is increasing, as is Alzheimer's in low- and middle-income countries, although this may depend on the improvement of diagnostic methods as well as the increase in aging population. A growing body of evidence highlighted potentially modifiable risk factors for dementia, such as suboptimal education, hypertension, hearing impairment, smoking, alcohol consumption, obesity, air pollution, depression, physical inactivity, diabetes, low social contact (Livingston et al., Lancet 2020; 396: 413–46). Post-diagnostic care for people with dementia should address physical and mental health, social care, and support. In the current status, pharmacological treatments represent only a (small) aspect of the multimodal approach to support people affected by dementia and their families. Treatments managing symptoms of Alzheimer's disease are on the market in several world regions, but none included on the WHO 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: Several systematic reviews on the use of donepezil in mild-to-moderate Alzheimer's diseases are published. Their results all indicated that when compared to placebo, donepezil showed statistically significant difference in cognitive outcomes and other functional measures. Below main results from the Cochrane Review published in 2018 with searches updated in May 2017 (Birks et al., Cochrane Database of Systematic Reviews 2018, Issue 6. Art. No.: CD001190) After 26 weeks of treatment, donepezil was found to be superior to placebo on the following outcomes: • Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog, range 0 to 70): mean difference (MD) -2.67, 95% confidence interval (CI) -3.31 to -2.02, 1130 participants, 5 studies; • Mini-Mental State Examination (MMSE) score: MD 1.05, 95% CI 0.73 to 1.37, 1757 participants, 7 studies; • Severe Impairment Battery (SIB, range 0 to 100): MD 5.92, 95% CI 4.53 to 7.31, 1348 participants, 5 studies; • Alzheimer's Disease Cooperative Study activities of daily living score for severe Alzheimer's disease (ADCS-ADL-sev): MD 1.03, 95% CI 0.21 to 1.85, 733 participants, 3 studies; • Improvement on the clinician-rated global impression of change scale: odds ratio (OR) 1.92, 95% CI 1.54 to 2.39, 1674 participants, 6 studies. No difference on behavioural symptoms and QoL. The quality of evidence was judged moderate for all the outcomes. A network meta-analysis evaluating the comparative effectiveness and safety of cognitive enhancers for Alzheimer's disease reported that for all effectiveness outcomes, donepezil+memantine is the most effective therapy, followed by donepezil and galantamine (Tricco et al., J Am Geriatr Soc 2018;66:170–178). Donepezil was found to be superior to placebo for the MMSE analysis (24 RCTs, 3,740 participants, MD = 1.39, 95% credible interval (CrI) = 0.53–2.24),) and ADAS-Cog analysis (21 RCTs, 3,293 participants, MD = -3.29, 95% CrI =-4.57 to -1.99). According to the authors, the effect size met criteria for minimally clinical important difference only for donepezil for the ADAS-Cog cognition outcome reported as a 3.1- to 3.8- point reduction). Results should be interpreted with caution as predictive intervals are sometimes wider that than the CrIs, suggesting that there is uncertainty regarding the effect size and CrI for these results. The same authors published a network meta-analysis with individual-participant level analysis to examine the comparative efficacy and safety of cognitive enhancers for patients with different characteristics, such as severities of Alzheimer's disease (Veroniki BMJ Open 2022;12:e053012). In this analysis donepezil +memantine (MD=2.57, 95% CI: 0.07 to 5.07), donepezil alone (MD=1.41, 95% CI: 0.51 to 2.32) improved MMSE score compared to placebo. The authors cited that MD larger than 1.40 is a minimal clinically important difference for MMSE. The point estimates and 95% CIs spanning between a mean decrease below and a mean increase above the suggested minimally clinical important difference affect any conclusion about the clinical value of donepezil. An important characteristic of the included trials is the use the last-observation-carried-forward strategy for intention-to-treat analysis when data were missing. This

	approach has been widely criticised especially in chronic conditions as Alzheimer's disease. Given that there are more dropouts from participants allocated to receive cognitive enhancers than placebo, this analysis could lead to bias favouring finding a positive outcome on cognition. Further important issues are duration of treatment, the severity of dementia and the effects of withdrawal at the end of the treatment period. The DOMINO study showed that, in people with moderate or severe Alzheimer's disease, continued treatment with donepezil was associated with modest cognitive and functional benefits donepezil over the course of 12 months relatively small compared to the overall size of the decline in cognitive and functional status that was seen this population (Howard et al., N Engl J Med 2012;366:893-903). Other analysis of studies with a follow-up of two or more years reported a high ratio of dropouts and inconclusive data on the clinical benefit of prolonged treatment, especially in people with concomitant medical illness, and polypharmacy (Franchi et al, Pharmacoepidemiology and drug safety 2011; 20: 497–505). After initial improvement, patients tended to decline linearly on all outcome measures, with those with worse MMSE score or more advanced age who tended to drop-out from treatment more easily. Uncontrolled observational studies have suggested the existence of a long-term stabilising effect that may reduce the rate of institutionalisation, but these results are likely to be skewed by indication biases (Lopez et al., J Am Geriatr Soc. 2005;53(1):83-7).
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: In general donepezil showed a good safety profile both in trials and clinical practice. Side effects are due to the stimulation of the cholinergic receptors of the peripheral nervous system: slowing of the heart rate and syncope, diarrhoea and/or nausea caused by increase of intestinal peristalsis that can lead to anorexia and long-term weight loss. The previously cited Cochrane Review reports that withdraw from the studies before the end of treatment was significantly higher with donepezil (24%) compared with placebo (20%) OR 1.25, 95% CI 1.05 to 1.50, 2846 participants, 12 studies. Adverse events during the studies were significantly more frequent with donepezil (72%) compared with placebo (65%) OR 1.59, 95% 1.31 to 1.95, 2500 participants, 10 studies.
Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable Comments: Clinical monitoring via an electrocardiograph (ECG) may be required in people with a pre-existing or family history of QTc prolongation.

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: Donepezil should be prescribed only in the settings where a specific dementia diagnosis can be made. There should be ongoing support and supervision by appropriately trained professionals with close monitoring of side effects and if possible, assessment of response by carers.
Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings?	☒ Yes ☐ No ☐ Not applicable Comments: According to the Applicant, the clear conclusion from the published studies, reviews and HTAs is that donepezil is more cost-effective than placebo when added to standard care for people with Alzheimer's disease. In many studies, donepezil is also found to lead to cost savings i.e., it 'dominates' its comparator in terms of both better outcomes and lower costs. Where donepezil has been compared to other acetylcholinesterase inhibitors, again it has usually been found to be the most cost-effective and has never been found to be less cost-effective than the other medications in this class. The available evidence comes almost entirely from high-income countries, but there is good reason to argue that donepezil would also be cost-effective in low- and middle-income countries through its effects on caregiver-related costs. Generics are available, with low price especially in low- and middle-income countries.
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: Anticholinesterase agents, including donepezil, are licensed since the 90s in more than 60 countries for the treatment of mild-to-advanced stages of Alzheimer's disease. According to WHO Global EML Database, 28 countries include donepezil in their national EML. According to the survey cited by the Application, most of the centres prescribed anti-dementia medications and in about 70% donepezil was the first line anti-dementia medication. A recent cross-sectional analysis of prescription in European countries showed a variable 10-year trend, with a steady decline in sales of AD drugs, mostly driven by France (Hassen JAMA Health Forum. 2022;3(8):e222253).

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) "Cholinesterase inhibitors and memantine may be offered for 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 (Conditional recommendation. Very Low quality of evidence)". According to the Application, updated guidelines will be published in 2023. It is unlikely that this recommendation will change.