A.8 Cytisine – EML

Reviewer summary	☒ Supportive of the proposal ☐ Not supportive of the proposal Justification (based on considerations of the dimensions described below): The public health relevance for tobacco cessation interventions is well established. Worldwide, nearly 1.25 billion people use tobacco. In 2020 global cigarette smoking prevalence was 36.7% for men and 7.8% for women. In 2022 around one billion people were smokers (15% of all people over 15 yrs). Tobacco is a major cardiovascular and respiratory risk factor, as well as for many types of cancer. Half of those who smoke long-term die from related causes; mortality is over 8 million people a year. Most of these deaths occur in LMIC as 80% of smokers live in those countries. More than half of those who smoke want to quit, however, nicotine in tobacco is addictive and less than 5% of unassisted quit attempts are sustained to 1 year. Three pharmacotherapies for tobacco cessation are currently on the WHO EML: NRTs, varenicline, and bupropion. The International Nonproprietary Name (INN) for cytisine is cytisinicline. Cytisine – cytisinicline - is listed in the WHO CC ATC DDD index under drugs used for nicotine dependence, with ATC code N07BA04. It is not a synthetic drug, but a plant-derived (*Laburnum anagyroides*) alkaloid and used for cessation of smoking since the 1960s in Europe. Cytisine binds selectively to α4β2 nicotinic acetylcholine receptors (nAChRs) in the central nervous system. It´s mode of action is similar to varenicline tartrate (it was a precursor for synthetic varenicline), but both have different half-lives and dosing regimens. Submission involves the WHO (Department of Health Promotion) and proposes inclusion of cytisine 1,5mg tablet as an individual medicine. The WHO's first Clinical Treatment Guideline for Tobacco Cessation, released on July 3, 2024, included cytisine along with NRT, varenicline, and bupropion, as effective tobacco cessation treatments. Nine letters of support from tobacco control and health promotion organizations, from Uruguai, US, Europe (European networks for tobacco control and cancer coalitions), Japan, Kenya, Southeast Asia and Jordan were presented. Overall, cytisine shows greater effectiveness than placebo and NRT and comparable effectiveness to varenicline. AE are lower than with varenicline, usually mild and self-limiting. Despite lack of sufficient evidence for cost-effectiveness, cytisine is reported as the cheapest smoking cessation medicine. It is available in 34 countries and presents two generic manufacturers. Due to shortages of varenicline and recalls by the main manufacturer caused by possible contamination with N-nitrosamines (N-nitroso- varenicline), cytisine may be a comparable alternative, in an indication where more feasible options are needed. These facts lead me to support the proposal of addition - as a square-box listing - of cytisine to the EML.
Does the EML and/or EMLc currently recommend alternative medicines for the proposed indication that can be considered therapeutic alternatives? Three pharmacotherapies for tobacco cessation are currently on the WHO EML: NRTs, varenicline, and bupropion. Alternatives currently listed in the EML are NRT in the form of patch, gum, lozenge, and mouth spray; bupropion (150 mg sustained-release), varenicline: 0.5 mg and 1 mg. (**https://list.essentialmeds.org/**)	☒ Yes ☐ No ☐ Not applicable
Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication? A Cochrane review[1] included 75 trials with 45,049 people. Moderate-certainty evidence (limited by heterogeneity) for superiority of cytisine to quit smoking over placebo (RR 1.30, 95% confidence interval (CI) 1.15 to 1.47; I2 = 83%; 4 studies, 4623 participants). Pooled results from randomised comparing cytisine or varenicline showed that more people in the varenicline arm quit smoking (RR 0.83, 95% CI 0.66 to 1.05; I2 = 0%; 2 studies, 2131 participants; moderate-certainty evidence). However, the evidence was limited by imprecision, and confidence intervals incorporated the potential for benefit from either cytisine or varenicline. Overall, cytisine shows greater effectiveness than placebo and NRT[2], and comparable[3]	☒ Yes ☐ No ☐ Not applicable

or inferior effectiveness to varenicline[4]. There seems to be no superior benefit of cytisine over varenicline[5]. A Real-world non randomized study showed less effectiveness than varenicline in a 40-week regimen[6].	
Does adequate evidence exist for the safety/harms associated with the proposed medicine? A Cochrane review[1] found no evidence of a difference in the number reporting SAEs (RR 1.04, 95% CI 0.78 to 1.37; I2 = 0%; 3 studies, 3781 participants; low-certainty evidence). SAE evidence was limited by imprecision. There was no data on neuropsychiatric or cardiac SAEs. Pooled results from randomised comparing cytisine or varenicline showed that more people in the varenicline arm reported SAEs (RR 0.67,95% CI 0.44 to 1.03; I2 = 45%; 2 studies, 2017 participants; low-certainty evidence). Cytisine showed more AE than placebo or NRT but less than varenicline[3]. A Real-world non-randomized study showed good tolerability of a 40-week regimen[6]. Adverse reactions to cytisine are moderate, non-serious, self-limiting and perhaps less frequent than in patients using other smoking cessation medicines.	☒ Yes ☐ No ☐ Not applicable
Overall, does the proposed medicine have a favourable and meaningful balance of benefits to harms? There is a positive benefit/risk ratio. The traditional dosing is a 25-day tapering regimen going from 9 to 1,5 to daily. A newer higher-dose regimen of 3 mg taken 3 times daily for 6 or 12 weeks also shows effectiveness and is well tolerated[7]. The course of treatment, which usually lasts 25 days, can be repeated to total a 2-month cycle. Studies show longer treatment with cytisine to be more effective than shorter duration.	☒ Yes ☐ No ☐ Not applicable
Are there any special requirements for the safe, effective and appropriate use of the medicines? Treatment success is optimized by counseling, and support from health care providers. For those who experience side effects with the standard regimens, a temporary or permanent dose reduction should be considered. Cytisine is not recommended for patients with impaired renal or hepatic function, under 18 or over 65 yrs of age, due to lack of evidence of safety and efficacy in those groups. High doses of cytosine are embryotoxic; cytisine is thus not recommended for use in pregnancy or lactation. Advanced atherosclerosis, some forms of schizophrenia, pheochromocytoma, severe impairment of the cardiovascular system and malignant hypertension are contraindications for use.	☒ Yes ☐ No ☐ Not applicable
Are there any issues regarding price, cost-effectiveness and budget implications in different settings? Cost-effectiveness is essential for a smoking cessation medicine that needs to be accessible to governments, institutions, and individuals in LMIC. However, despite the perception of cytisine cost-effectiveness, only one completed study of cost-effectiveness comparing cytisine with placebo showed no gain for cytisine. Nevertheless, different HTA bodies have concluded that treatment with cytisine has an acceptable cost-benefit profile. Evidence is its reimbursement status in countries across North America, Europe, Africa, the Middle East, and Asia Pacific. Cytisine is reported as the cheapest smoking cessation medicine, cheaper than NRT and bupropion. A 12-wk treatment in six Europea countries shows an average price reduction of 41.5% in comparison to varenicline.	☒ Yes ☐ No ☐ Not applicable
Is the medicine available and accessible across countries? Cytisine is mostly available in 1.5 mg tablets or film-coated tablets, or hard capsules. In specific countries, it is sold either as prescribed medicine, or OTC product and sold with local tradenames: Asmoken, Belnifrem, Cerdablan, Citidaron, Citisiniclina, Cytisinicline, Adamed, Cravv, Cytisine, Cytisinum Aflofarm, Decigatan, Defucitan, Defumoxan, Desmoxan, Dextazin, Heavis, Jablerdiz, Kobayzaren, Liberisan, Liberizin, Novynta, Recigar, Tabex, Todacitan, Tokovys, Xistab, Zandraqet. There are two manufacturers of generic cytisine; however availability is limited to European countries, a few Asian and one African country.	☐ Yes ☒ No ☐ Not applicable

Does the medicine have wide regulatory approval? Cytisine is not approved by the FDA. It is registered in 34 countries, mostly European, with some Asian and one African country: Armenia, Austria, Azerbaijan, Belgium, Bulgaria, Canada, Czech Republic, Denmark, Georgia, Germany, Greece, Hungary, Ireland, Italy, Kazakhstan, Latvia, Lithuania, Malta, Mongolia, Netherlands, North Macedonia, Poland, Portugal, Romania, Russian Federation, Serbia, Slovakia, Spain, Sweden, Thailand, Ukraine, United Kingdom, Uzbekistan, Zambia. Due to shortages of varenicline and recalls by the main manufacturer caused by possible contamination with N-nitrosamines (N-nitroso- varenicline), cytisine may be a comparable alternative[8].	☐ Yes, for the proposed indication ☐ Yes, but only for other indications (off-label for proposed indication) ☒ No ☐ Not applicable

Additional References

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