A.8 Cytisine – EML

Reviewer summary	☒ Supportive of the proposal ☐ Not supportive of the proposal Justification (based on considerations of the dimensions described below): Smoking is a huge global problem, resulting in several diseases: The importance of quitting is obvious, but the success rate remains low. "The drug has been used since the 1950s in, among other places, former Soviet states. However, there was relatively little RCT evidence. In recent years, a lot of additional RCT evidence has been published, as well as Cochrane reviews, which show favorable results in terms of both effectiveness and safety. The first-line approach to quitting smoking is education and counseling. If this proves insufficient, pharmacological support can be considered, including nicotine replacement therapies, which can increase the chances of successfully quitting from around 10% to approximately 15%. Cytisinicline, a partial nicotine agonist similar to varenicline, is an alternative to nicotine replacement therapies. Of the 14 studies, 12 reported higher rates of tobacco cessation among participants receiving cytisine (1.5 mg) or (3 mg) compared to placebo, compared to varenicline, compared to NRT, and compared to counseling. In 2024 WHO published a clinical treatment guideline for tobacco cessation in adults, which recommends: varenicline, NRT, bupropion, and cytisine as pharmacological treatment options for people who smoke and want to quit. There are contraindications. It is not approved by EMA, FDA 2024 Breakthrough Therapy designation**,** Regulatory approval in 34 countries Side effects acceptable Not prescribed <18 and > 65 years of age. HTA bodies in several markets have concluded that treatment with cysine has an acceptable cost-benefit profile as evidenced by its reimbursement status in countries across several regions. Alternatives such as varenicline have faced significant availability issues in recent years, see for example: https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(23)00184-4/fulltext
Does the EML and/or EMLc currently recommend alternative medicines for the proposed indication that can be considered therapeutic alternatives? (**https://list.essentialmeds.org/**)	☒ yes ☐ No ☐ Not applicable. The WHO) Model List of Essential Medicines (EML) includes for smoking cessation: Nicotine Replacement Therapy (NRT): on EML since 2009. Bupropion: Added to the EML in 2021, it is an antidepressant that reduces cravings and withdrawal symptoms. Varenicline: Added to the EML in 2021, varenicline works by reducing cravings.

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Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication? (e.g., evidence originating from multiple high-quality studies with sufficient follow up. This may be evidence included in the application, and/or additional evidence identified during the review process;) There is substantial evidence supporting the efficacy of cytisine as an aid for smoking cessation. Recent systematic reviews and meta-analyses have reinforced its effectiveness:	☒ Yes ☐ No ☐ Not applicable Ofori S, et al. Cytisine for smoking cessation: A systematic review and meta-analysis. Drug Alcohol Depend. 2023 ;251:110936. Hajek P, et al. Efficacy of cytisine in helping smokers quit: systematic review and meta-analysis. Thorax. 2013 ;68(11):1037-42.
Does adequate evidence exist for the safety/harms associated with the proposed medicine? (e.g., evidence originating from multiple high-quality studies with sufficient follow up. This may be evidence included in the application, and/or additional evidence identified during the review process;) There is substantial evidence from multiple studies regarding the safety profile of cytisine as a smoking cessation aid. While cytisine has been associated with certain adverse events, these are generally mild to moderate in severity. A 2023 systematic review and meta-analysis reported that cytisine increased the occurrence of AEs, primarily gastrointestinal issues, compared to placebo. However, these were mostly mild to moderate in severity. The same 2023 review found that cytisine was associated with a higher incidence of AEs compared to NRT, with gastrointestinal symptoms being the most common. Despite this, the overall safety profile was considered acceptable. Cytisine was associated with fewer adverse events compared to varenicline. A 2014 study comparing cytisine to NRT therapy found that AEs were more frequently reported in the cytisine group. These events were primarily self-reported and included symptoms such as nausea and vomiting, and sleep disorders. The majority of these AEs were non-serious and mild to moderate in severity.	☒ Yes ☐ No ☐ Not applicable Zatoński W, Zatoński M. Cytisine versus nicotine for smoking cessation. N Engl J Med. 2015;372:1072. Walker N et al. Cytisine versus nicotine for smoking cessation. N Engl J Med 2014;371:2353-2362
Overall, does the proposed medicine have a favourable and meaningful balance of benefits to harms?	☐ Yes ☐ No ☐ Not applicable
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) Contraindications several, including: • Cardiovascular conditions: Unstable angina, recent myocardial infarction, or clinically significant arrhythmias. • Cerebrovascular events: Recent stroke. • Pregnancy and breastfeeding AEs: Common side effects: • Gastrointestinal symptoms: nausea, vomiting, dry mouth, dyspepsia, constipation, or diarrhea. • Neurological symptoms: Dizziness, drowsiness, sleep disorders, or headaches. • Psychological symptoms: mood changes, anxiety, or irritability. • Cardiovascular symptoms: Hypertension or tachycardia. Patients should be monitored for adverse reactions, and any severe or persistent side effects should prompt consultation with a healthcare professional.	☒ Yes ☐ No ☐ Not applicable

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Are there any issues regarding price, cost-effectiveness and budget implications in different settings?	☐ Yes ☒ No ☐ Not applicable
Is the medicine available and accessible across countries? (e.g. shortages, generics and biosimilars, pooled procurement programmes, access programmes) Cytisine, is not EMA-approved. EMA Approval Status: Cytisinicline has not received centralized approval from the EMA. Medicines not centrally approved by the EMA may still be authorized at the national level within individual European countries. Colleagues in low- and middle-income countries indicated that if it is added to the Essential Medicines List (EML), the likelihood of it becoming available in their countries increases.	☐ Yes ☒ No ☐ Not applicable
Does the medicine have wide regulatory approval? Not EMA and but in October 2024, the FDA granted cytisinicline Breakthrough Therapy Designation. Regulatory approval in 34 countries	☐ Yes, for the proposed indication ☐ Yes, but only for other indications (off-label for proposed indication) ☒ No But FDA granted Breakthrough Therapy Designation ☐ Not applicable