Cytisine (cytisinicline)
Essential medicine status
Section:
24. Medicines for mental and behavioural disorders 24.5. Medicines for disorders due to psychoactive substance use 24.5.2. Medicines for nicotine use disorders
ATC codes: N07BA04
Indication
Nicotine dependence ICD11 code: 6C4A.2
Medicine type
Chemical agent
List type
Core
Formulations
Oral > Solid > tablet: 1.5 mg
EML status history
First added in 2025 (TRS 1064)
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
Cytisine (cytisinicline)
DrugBank
Cytisine
Expert Committee recommendation
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The Expert Committee recognized the important public health relevance of effective interventions for tobacco cessation, given the significant public health burden associated with smoking and tobacco use globally. The Committee noted that the EML currently includes multiple pharmacological treatment options for tobacco cessation (nicotine replacement therapy, bupropion and varenicline). The Committee agreed that the availability of a variety of effective treatment options can be beneficial in terms of offering choice for individuals wishing to quit, recognizing that quit attempts are often unsuccessful or are not sustained in the long term. The Committee also recognized the value of having multiple options available in the context of shortages, such as that reported in recent years for varenicline. The Committee considered that the evidence presented in the application from three recent systematic reviews, with comparisons versus placebo and versus active comparators, supported the benefits of cytisine as an effective intervention for tobacco cessation as measured by abstinence rates. No serious safety concerns were identified, with adverse events being generally mild and manageable. Overall, the Committee considered that the balance of benefits to harms for cytisine was favourable. The Committee noted that cytisine has limited global availability, but in settings where it is available, treatment costs are reportedly lower than for nicotine replacement therapy and varenicline. The Committee also noted that in low- and middle-income settings, tobacco cessation treatments, including cytisine, have been reported to be more expensive than smoking, and that cytisine in particular was determined not to be cost-effective. However, in high-income settings, it has been determined to be cost-effective. The Committee also noted that the first invitation to manufacturers of medicinal products for treatment of disorders caused by use of tobacco to submit an expression of interest for WHO prequalification was published in 2023. The invitation is currently limited to nicotine replacement therapy (gum and transdermal patches) but other medicinal products on the EML could be added to this invitation in the future. The Committee considered that WHO prequalification of cytisine, bupropion and varenicline could support greater access and availability of quality-assured tobacco cessation products. The Committee welcomed the publication in 2024 of the WHO guidelines for tobacco cessation, in which cytisine has a strong recommendation based on moderate-certainty evidence as a pharmacological treatment option for tobacco users interested in quitting. Based on these considerations, the Expert Committee recommended the addition of cytisine to the core list of the EML as a treatment option for tobacco and smoking cessation. The Committee stressed the importance of counselling and behavioural support, in addition to pharmacotherapy, as part of comprehensive tobacco and smoking cessation efforts.
Background
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Cytisine has not previously been evaluated for inclusion on the EML. Three pharmacotherapies for tobacco cessation are currently on the EML: nicotine replacement therapy (patch, gum, lozenge and mouth spray), bupropion and varenicline. The International Nonproprietary Name for cytisine is cytisinicline. The name cytisine is used throughout the application because it is more widely recognized globally. It is also the name used in the WHO guideline for tobacco cessation in adults.
Public health relevance
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The public health relevance for tobacco cessation interventions is well established. Tobacco use is a major risk factor for cardiovascular and respiratory diseases, more than 20 different types or subtypes of cancer and many other debilitating health conditions. In 2020, 22.3% of the world’s population used tobacco: 36.7% of men and 7.8% of women. Most (80%) of the 1.3 billion tobacco users globally live in low- and middle-income countries. Annually, more than 8 million people die from tobacco use, with most tobacco-related deaths occurring in low- and middle-income countries. To address the tobacco epidemic, WHO Member States adopted the Framework Convention on Tobacco Control (FCTC) in 2003. Currently 182 countries are Parties to this treaty (1). Over 60% of people who smoke say they want to quit (2). Less than 5% of unassisted quit attempts are sustained to 1 year (3). As most quit attempts are

unsuccessful and relapse is a hallmark of addiction, people who smoke and want to quit need access to a variety of options including behavioural interventions and pharmacological treatments.

Benefits

The application presented findings from a literature search to identify cumulative reports that evaluated randomized controlled trials of cytisine with placebo, comparisons with other smoking cessation medications, or studies that tested different doses for smoking cessation. A 2024 systematic review and meta-analysis of 14 randomized controlled trials evaluated the effectiveness of cytisine for tobacco cessation, and the effects of dose and concomitant use of behavioural or other pharmacological interventions on cessation outcomes (4). For the comparison of cytisine versus placebo or no intervention, there was moderate-certainty evidence that cytisine was associated with increased abstinence rates (24.0% versus 17.4%; risk ratio (RR) 2.65, 95% confidence interval (CI):1.50 to 4.67; six randomized controlled trials, 5194 participants). For the comparison of cytisine versus nicotine replacement therapy, there was moderate-certainty evidence that cytisine was associated with increased abstinence rates (21.2% versus 15.5%; RR 1.36, 95% CI 1.06 to 1.73; two randomized controlled trials, 1511 participants). For the comparison of cytisine versus varenicline, there was low-certainty evidence of no significant difference in abstinence rates at 6 months between treatment groups (11.9% versus 11.6%; RR 0.96, 95% CI 0.63 to 1.45; three randomized controlled trials, 2508 participants). For the comparison of 6 weeks versus 12 weeks of cytisine treatment, there was moderate-certainty evidence that participants who received a longer duration of treatment were significantly more likely to quit smoking compared to participants who received a shorter duration of treatment (22.9% versus 18.3%; RR 1.29, 95% CI 1.02 to 1.63; two randomized controlled trials, 1009 participants). A 2023 Cochrane systematic review and meta-analysis of 75 randomized controlled trials (45 049 participants) evaluated the effectiveness of nicotine receptor partial agonists for smoking cessation (5). The review included eight randomized controlled trials (almost 9000 participants) involving cytisine. Of these studies, four compared cytisine with placebo, two were comparisons with varenicline, one was a comparison with nicotine replacement therapy, and one was a dosing variation study. The review found moderate-certainty evidence that cytisine helped more people quit smoking compared with placebo as measured by smoking abstinence at longest follow-up (RR 1.30, 95% CI 1.15 to 1.47; four randomized controlled trials, 4623 participants). For the comparison of cytisine versus varenicline, there was moderate-certainty evidence of no significant difference in abstinence rates between treatments (RR 0.83, 95% CI 0.66 to 1.05; two randomized controlled trials, 2131 participants). For the comparison of cytosine versus nicotine replacement therapy, there was low-certainty evidence of greater benefit of cytisine (RR 1.43, 95% CI 1.13 to 1.80; one randomized controlled trial 1310 participants). A 2023 Cochrane systematic review and component network meta-analysis of 319 clinical trials (157 179 participants) evaluated the comparative benefits of established pharmacotherapies and e-cigarettes as smoking cessation interventions (6). Among pharmacotherapies, there was high-certainty evidence that: varenicline (odds ratio (OR) 2.23, 95% credible interval (CrI) 2.02 to 2.68; 67 randomized controlled trials, 16 430 participants); cytisine (OR 2.21, 95% CrI 1.66 to 2.97; seven randomized controlled trials, 3848 participants); nicotine patch (OR 1.37, 95% CrI 1.20 to 1.56; 105 randomized controlled trials, 37 319 participants); fast-acting nicotine replacement therapy (OR 1.41, 95% CrI 1.29 to 1.55; 120 randomized controlled trials, 31 756 participants); and bupropion (OR 1.43, 95% CrI 1.26 to 1.43; 71 randomized controlled trials, 14 759 participants) were associated with significantly greater likelihood of abstinence at 6 months compared with placebo.

Harms

The most frequently reported adverse events associated with cytisine include gastrointestinal disturbances and sleep disorders (7). From the 2024 systematic review and meta-analysis of cytisine for tobacco cessation, higher (but non-significant) rates of adverse events were seen between cytisine and placebo (RR 1.19, 95% CI 0.99 to 1.42; six randomized controlled trials, 4578 participants) and between cytisine and varenicline (RR 1.37, 95% CI 0.57 to 3.33; two randomized controlled trials, 1345 participants). Most adverse events were reported as mild (4). The 2023 Cochrane systematic review of nicotine receptor partial agonists for smoking cessation assessed harms at the participant level. Analysis of non-serious adverse events found a slight increase in patients receiving cytisine versus placebo (RR 1.22, 95% CI 1.07 to 1.39; four randomized controlled trials, 4052 participants). In an analysis of serious adverse events, no significant difference was seen between cytisine and placebo (RR 1.04, 95% CI 0.78 to 1.37; three randomized controlled trials, 3781 participants). For the comparison of cytisine and varenicline, there was low-certainty evidence of a trend towards fewer serious adverse events with cytisine (RR 0.67, 95% CI 0.44 to 1.03; two randomized controlled trials, 2017 participants). For the comparison of cytisine and nicotine replacement therapy, no significant difference was seen in the rate of serious adverse events between treatment groups (RR 1.15, 95% CI 0.76 to 1.75). Study-related neuropsychiatric or cardiac serious adverse events were not reported (5). From the 2023 Cochrane systematic review of established pharmacotherapies and e-cigarettes as smoking cessation interventions, there was low-certainty evidence of no significant difference in serious adverse events compared to placebo for varenicline, cytisine, single-form nicotine replacement therapy and combination nicotine replacement therapy.

Cost / cost effectiveness

Health technology assessment bodies in several markets have concluded that treatment with cytisine has an acceptable cost–benefit profile as evidenced by its reimbursement status in countries in a number of regions. However, it has been highlighted that smoking cessation treatments are more expensive than smoking in many settings, particularly in low- and middle-income countries (9). A 2020 trial-based cost-utility analysis evaluated the cost–effectiveness of cytisine versus placebo in addition to brief behavioural support for smoking cessation in 2472 patients newly diagnosed with tuberculosis in hospitals in Bangladesh and Pakistan (10). Mean total costs were higher in the cytisine group, while mean quality-adjusted life years (QALYs) were lower over 6 months. Thus, cytisine was dominated by placebo and it was concluded not to be cost-effective. A 2014 modelled cost–effectiveness analysis from the United Kingdom evaluated the cost–effectiveness of cytisine compared with varenicline for smoking cessation (11). The analysis was limited by the identification of only two trials and the absence of manufacturer cost data for cytisine. Cytisine was assumed to be less costly and more effective than varenicline (i.e. dominant). A 2018 study estimated the cost–effectiveness from a health-care perspective of introducing national level changes to smoking cessation services in England and the Netherlands, namely introduction of cytisine, increasing brief physician advice, increasing behavioural support with quitting and all changes implemented together (12). Costs and QALYs generated by those changes over 2, 5, 10 years and a lifetime were compared with those of current practice in each country. The combined change of adding all three cessation

services was dominant over all alternative changes in both countries and would generate an incremental net benefit of 11.47 euros (€) and €9.96 per smoker over 2 years and of €56.16 and €60.72 per smoker over a lifetime in the Netherlands and England, respectively. The application presented a comparison of costs for 12 weeks of treatment with cytisine versus other smoking cessation therapies in selected European countries (Table 13). Table 13. Twelve-week treatment cost of smoking cessation therapies in Europe Treatment Cost per person, € Denmark Italy Portugal Spain Sweden United Kingdom Cytisine 200 99 100 112 95 135 NRT patch 310 256 230 216 239 215 NRT spray 608 504 570 570 665 760 Varenicline 313 340 156 279 166 139 €: euro; NRT: nicotine replacement therapy; United Kingdom: United Kingdom of Great Britain and Northern Ireland.

WHO guidelines

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The 2024 WHO guidelines for tobacco cessation include a strong recommendation for cytisine as a pharmacological treatment option for tobacco users who smoke and are interested in quitting (8). The certainty of evidence for cytisine was considered moderate based on several factors including the variability in dosing, the small number of countries that have approved the medicine and the absolute number of studies that have evaluated treatment in different sociodemographic groups. The guideline highlights the potential for implementation of cytisine based on large benefits, small harms and lower cost.

Availability

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The application reported that cytisine currently has regulatory approval as either a prescription or over-the-counter product in 34 (mostly high-income) countries globally.

Other considerations

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The Department of Health Promotion reviewed and provided comments on the application. The technical department supported the inclusion of cytisine on the EML, highlighting that inclusion would increase the choice of cessation options for tobacco users who want to quit. The department considered that the application was supported by high population needs, strong evidence on efficacy and safety, and comparative cost–effectiveness.

☐ Show references Hide references

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