APPLICATION FOR THE INCLUSION OF CYTISINE ON THE WHO MODEL LIST OF ESSENTIAL MEDICINES FOR THE TREATMENT OF NICOTINE DEPENDENCE AS AN AID TO STOPPING SMOKING AND TOBACCO USE

Applicants:

Raymond G. Boyle, PhD, MPH
Independent Researcher
Minneapolis, MN

Judith J. Prochaska, PhD, MPH
Professor of Medicine
Deputy Director, Stanford Prevention Research Center
Department of Medicine | Stanford University

Krzysztof Przewozniak, PhD, MA
Professor
Global Institute of Family Health
Calisia University, Kalisz, Poland
Affiliated Faculty / External Expert, University of Southern California, Los Angeles, CA, USA

Department of Health Promotion
World Health Organization, Geneva

Persons to contact:
Raymond G. Boyle, PhD, MPH
Email:rboyle7@gmail.com
Phone: +1 612-636-0870

Judith J. Prochaska, PhD, MPH
Email:jpro@stanford.edu
Phone: +1 650-724-3608

Date of submission:
31 October 2024

Section 1: Summary statement of the proposal

This application is designed to support the inclusion of cytisine[1] on the core list of the World Health Organization Essential Medicines List (WHO EML) for the treatment of nicotine dependence as an aid to stopping smoking and tobacco use in adults. The significant worldwide burden of illness imposed by tobacco use, and the reduction in that burden achieved by quitting, are both well-documented, placing tobacco cessation among the most valuable of public health interventions *(1, 2)*. Worldwide, nearly 1.25 billion people use tobacco and more than 8 million people die annually from tobacco related diseases *(1, 3)*. People who smoke and want to quit need access to a variety of cessation aids. Only three pharmacotherapies for tobacco cessation are currently on the WHO EML: NRTs, varenicline, and bupropion.
In this application, we consider the best available evidence on efficacy and acceptability of cytisine, as compared to placebo or alternative pharmacological interventions, for smoking cessation in adults. In addition, the safety data for cytisine from these clinical trials are reviewed, and the cost-effectiveness data are presented.

Cytisine has been demonstrated to be an effective aid to smoking cessation that is comparable to varenicline and superior to combination NRT (patch plus gum or lozenges) both in head-to-head studies and in the Cochrane meta-analyses. As such, cytisine warrants inclusion on the core list of the WHO EML.

Section 2: Consultation with WHO technical departments

WHO No Tobacco Unit (TFI), Health Promotion Department focal point being Dr. Vinayak Mohan Prasad email: prasadvi@who.int

Section 3: Other organizations consulted or supporting the submission

Aflofarm and Adamed, two Polish pharmaceutical companies manufacturing generic cytisine, provided information on the number of countries with regulatory approvals for cytisine.

Letters of support from nine organizations who support the submission have been obtained, please see the letters in the Annex

Section 4: Key information summary for the proposed medicine

INN	Cytisine (cytisinicline)		
ATC code	N07BA04		
Indication	Smoking cessation in adults		
ICD-11 code	6C4A.2Z Nicotine dependence		
Dosage form	**Strength**	**EML**	**EMLc**
Solid oral	1.5 mg	Yes	No

[1]Cytisine is the original botanical compound. The International Nonproprietary Name (INN) for cytisine is cytisinicline. Cytisine is used consistently throughout this document because it is widely recognized all over the world and the WHO clinical treatment guideline for tobacco cessation in adults refers to cytisine.

Section 5: Listing as an individual medicine or representative of a pharmacological class / therapeutic group

This submission is a proposal to list cytisine as an individual medicine.

Section 6: Information Supporting the Public Health Relevance

The public health relevance for tobacco cessation interventions is well established. The global burden of disease due to tobacco use is extensive and well characterized by the WHO with the following statistics (https://www.who.int/news-room/fact-sheets/detail/tobacco):

- Nicotine contained in tobacco is highly addictive
- In 2020, 22.3% of the world's population used tobacco: 36.7% of men and 7.8% of women
- In 2022, the global cigarette smoking prevalence was 15.0% among all persons aged 15 years and older, which is nearly a billion people
- Tobacco kills up to half of people who smoke long-term
- Tobacco smoking use is a major risk factor for cardiovascular and respiratory diseases, over 20 different types or subtypes of cancer, and many other debilitating health conditions
- Annually, more than 8 million people die from tobacco use
- 80% of the world's 889.7 million people who smoke cigarettes live in low- and middle-income countries
- Most tobacco-related deaths occur in low- and middle-income countries, which are often targets of intensive tobacco industry interference and marketing
- 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
- The WHO MPOWER measures are in line with the WHO FCTC and have been shown to save lives and reduce costs from averted healthcare expenditure. The O in MPOWER stands for offer help to quit tobacco use.

Over 60% of people who smoke say they want to quit *(4)*. Yet, for most people who smoke, it is not a lifestyle choice or habit but driven by an addiction to nicotine. Less than 5% of unassisted quit attempts are sustained to 1 year *(5)*. 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 behavioral interventions and pharmacological treatments. The WHO clinical treatment guideline for tobacco cessation in adults recommends varenicline, NRT, bupropion, and cytisine as pharmacological treatment options for people who smoke and are interested in quitting *(6)*.

Currently, the WHO Essential Medicines List includes the following medications for this indication and target population:

- NRT in the form of patch, gum, lozenge, and mouth spray
- Bupropion (150 mg sustained-release)
- Varenicline: 0.5 mg and 1 mg

This submission provides an additional medication for adults who want to quit smoking.

Section 7: Treatment details (requirements for diagnosis, treatment and monitoring).

Usual Dosage for Adults

Cytisine is indicated as an aid to quit smoking in adults 18 years and older *(7, 8)*. The efficacy of cytisine in smoking cessation is believed to be the result of its activity at the α4β2 sub-type of the nicotinic receptor family *(9)*. Varenicline has a similar mechanism of action, though is synthetically derived, while cytisine is derived from botanical sources.

The success of medications for quitting smoking is optimized when patients are prepared to quit and receive quit advice, counseling, and support from health care providers. Patients who smoke tobacco should be encouraged to set a quit date.

The recommended course of treatment for cytisine starts at 1.5 mg every two hours (maximum of six doses per day) for days 1–3, tapered gradually, with a scheduled quit date at day 5, and ending with 1.5 mg once or twice daily by days 21-25 (see Table 1). 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 with more patients giving up smoking.

When using cytisine to quit smoking, the patient should set a target quit date within the first week of starting the medication. Treatment is initiated while the patient is still smoking, because approximately 1 week of treatment is required to achieve steady-state blood levels.

Table 1. Dosing Schedule Summary: Cytisine

Days	Medication Dose & Smoking Schedule
1-3	1.5 mg every 2 hours (6 tablets/day max), reducing in parallel the number of cigarettes smoked daily
4-12	1.5 mg every 2.5 hours (5 tablets/day max), with cessation by day 5
13-16	1.5 mg every 3 hours (4 tablets/day max)
17-20	1.5 mg every 5 hours (3 tablets/day max)
21-25	1.5 mg taken 1 or 2 times daily (2 tablets/day max)

For patients who experience side effects with the standard regimens, a temporary or permanent dose reduction should be considered in consultation with their physician.

Patients who failed in stopping smoking during prior cytisine therapy for reasons other than intolerability due to adverse events (AEs) or who relapsed after treatment, should be encouraged to make another quit attempt with cytisine once factors contributing to the failed attempt have been identified and addressed.

Dosage in Special Populations

Patients with Impaired Renal or Hepatic Function
Lacking clinical experience of cytisine in patients with impaired renal or hepatic impairment, the medication is not recommended for this patient population.

Elderly Population
Due to limited clinical experience, cytisine is not recommended for use in patients over the age of 65 years.

Pediatric Population
Cytisine use is not recommended for use in pediatric patients because the safety and efficacy of cytisine in people under 18 years of age have not been established.

Pregnancy and Lactation
Based upon animal research with higher doses of the drug leading to embryotoxic action, cytisine is not recommended for use in pregnancy, in case of uncontrolled administration, or during breast feeding.

Other Contraindications: Advanced atherosclerosis, some forms of schizophrenia, pheochromocytoma, conditions connected with severe impairment of the cardiovascular system and malignant hypertension

Section 8: Review of Evidence for Benefits and Harms

Benefits
In this section the scientific evidence for benefits is presented. A search was completed to identify cumulative reports that evaluated randomized controlled trials of cytisine/cytisinicline with placebo, comparisons with other smoking cessation medications, or studies that tested different doses for smoking cessation. This search reviewed cumulative reports from the Cochrane Database of Systematic Reviews, the WHO Clinical Trial Registry, and a PubMed citation search for randomized trials.

Search string used for PubMed:
(("smoking cessation"[Title/Abstract] OR "smoking cessations"[Title/Abstract] OR "tobacco use cessation"[Title/Abstract] OR "smok*"[Title/Abstract] OR "tobacco"[Title/Abstract] OR "quit smok*"[Title/Abstract] OR "cessation"[Title/Abstract] OR "stopping"[Title/Abstract] OR "abstinen*"[Title/Abstract] OR "tobacco use cessation"[MeSH Terms] OR "smoking cessation"[MeSH Terms] OR "smoking/prevention and control"[MeSH Terms] OR "smoking/therapy"[MeSH Terms] OR "tobacco"[MeSH Terms] OR "smoking"[MeSH Terms] OR "tobacco products"[MeSH Terms] OR "tobacco use"[MeSH Terms] OR "nicotine"[MeSH Terms]) AND "Cytisine"[Title/Abstract] OR “Tabex”[Title/Abstract] AND ("randomized controlled trial"[Title/Abstract] OR "randomised controlled trial"[Title/Abstract] OR "randomized clinical

trial"[Title/Abstract] OR "randomised clinical trial"[Title/Abstract] OR "RCT"[Title/Abstract] OR "randomized controlled trials as topic"[MeSH Terms] OR "randomized controlled trials as topic"[MeSH Terms] OR "randomized controlled trials as topic"[MeSH Terms] OR "random allocation"[MeSH Terms]))

From a few studies reported in the 1970s, there are now 14 high-quality randomized controlled trials that contributed to the cytisine evidence base in 2024. In an early review of the literature on cytisine for smoking cessation, Etter *(10)* examined the studies completed between 1967 and 2005, but found generally low-quality studies with only 1 randomized controlled trial. In 2007, the first Cochrane systematic review of nicotine receptor partial agonists for smoking cessation was published *(11)*. This report set the baseline, because the first clinical trials of varenicline were being published. The Cochrane authors included in their review the early controlled trial with cytisine *(12)* but noted the use of self-reported point prevalence abstinence without biochemical verification. However, this study reported outcome data up to 2 years with a positive effect for cytisine.

The Cochrane systematic review of nicotine receptor agonists has been updated several times. The 2016 update *(13)* included 4 trials of cytisine for smoking cessation, with two trials that verified self-reported abstinence. Those 2 trials *(14, 15)* compared cytisine with placebo across 937 participants with 470 taking active drug. There was a significant benefit in favor of cytisine (RR = 3.98 95% CI = 2.01 to 7.87). The other study was a non-inferiority trial with a large sample of telephone quitline participants (N=1360) *(16)*. It found a significant benefit for cytisine over NRT (RR = 1.43 95% CI = 1.13 to 1.80). NRT offered was the nicotine patch combined with gum or lozenge. The absolute quit rates for these early trials were modest and additional studies were deemed necessary to support a higher degree of certainty of a positive effect.

In 2023, the Cochrane review of nicotine receptor agonists was updated with studies through April 2022 *(17)*. This update added 4 trials to the earlier review for a total of 8 studies with almost 9000 participants. Of these studies, 4 compared cytisine with placebo, 2 involved a comparison with varenicline, 1 was a comparison with NRT and 1 was a dosing variation of cytisine. In their overall conclusion the authors found that cytisine helped more people quit smoking compared to placebo, RR = 1.30 (95% CI = 1.15 to 1.47). Based on the studies that randomized participants to cytisine or varenicline, there was no evidence of a difference in quit rates (RR = 1.00, 95% CI = 0.79 to 1.26).

The most recent systematic review and meta-analysis was published on 4 July, 2024 *(18)* and is therefore included as a comprehensive update from the previous Cochrane review. This review added 6 new studies for a total of 14. These 14 studies have been conducted in a wide range of geographic locations including Australia, Bangladesh and Pakistan, Croatia and Slovenia, Germany, Italy, Kyrgyzstan, New Zealand, Poland, Russia, Thailand, and the United States. Eight studies compared cytisine to placebo, three to varenicline, two with NRT, and one with counseling and information about quit aids.

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 *(19)*, compared to NRT *(16)*, and compared to counseling *(20)*.

Cytisine vs Placebo

In the meta-analysis of 6 trials *(18)*(Table 2), cytisine increased abstinence (665/2770, 24%) compared to placebo or untreated control condition (422/2424, 17.4%) (RR = 2.65, 95% CI = 1.50-4.67, 6 trials, 5194 participants). Three other placebo-controlled trials did not meet inclusion criteria for the analysis. The certainty of evidence was considered moderate with one study deemed at serious risk of bias.

Table 2. Cytisine vs Placebo Quit Rates

	Intervention		Comparison		RR (95% CI)
Study	Participants	Abstinent	Participants	Abstinent	
Dogar 2020	1239	401	1233	366	1.09 (0.97-1.23)
Phusahat 2022	67	11	65	6	1.78 (0.70-4.53)
Vinnikov 2008	85	9	86	1	9.11 (1.18-70.3)
West 2011	370	37	370	13	2.85 (1.54-5.27)
Pastorino 2022	470	151	399	29	4.42 (3.04-6.43)
Rigotti 2023	539	56	271	7	4.02 (1.86-8.71)
	2770	**665**	**2424**	**422**	**2.65 (1.50-4.67)**

All outcomes were self-reported with biochemical verification
Tobacco Abstinence ranged from 22 weeks to 48 weeks
Source: Puljević et al., 2024

Cytisine vs Nicotine Replacement Therapy

Two trials compared cytisine to NRT *(16, 21)* (Table 3). In the pooled meta-analysis across these trials *(18)*, participants who received cytisine were more likely to quit smoking (160/755, 21.2%) compared to receiving NRT (117/756, 15.5%) (RR = 1.36, 95% CI = 1.06-1.73). The certainty level was considered moderate for these trials.

Table 3. Cytisine vs NRT Quit Rates

	Intervention		Comparison		RR (95% CI)
Study	Participants	Abstinent	Participants	Abstinent	
Tindle 2022	100	17	101	17	1.01 (0.55-1.86)
Walker 2014	655	143	655	100	1.43 (1.13 -1.80)
	755	**160**	**756**	**117**	**1.36 (1.06-1.73)**

Outcomes were self-reported with 1 study using biochemical verification
Abstinence at 6 months was defined as 7 days point prevalence and continuous abstinence
Source: Puljević et al., 2024

Cytisine vs Varenicline

Three trials were included in the meta-analysis comparing cytisine with varenicline *(18)* (Table 4). There were no significant differences in the comparison of abstinence at 6 months, 11.9% vs

11.6% (RR = 0.96, 95% CI = 0.63-1.45). The certainty of evidence from the three studies was considered low because of imprecision and unexplained heterogeneity.

Table 4. Cytisine vs Varenicline Quit Rates

	Cytisine		Varenicline		RR (95% CI)
Study	Participants	Abstinent	Participants	Abstinent	
Courtney 2021	725	85	727	97	0.88 (0.67-1.15)
Oreskovic 2023	186	43	191	62	0.71 (0.51-0.99)
Walker 2021	337	41	342	27	1.54 (0.97-2.45)
	1248	**169**	**1260**	**186**	**0.96 (0.63-1.45)**

Outcomes were self-reported; 1 study biochemical verified
Abstinence at 6 months was defined as 7 days point prevalence and continuous abstinence at quit date
Source: Puljević et al., 2024

Treatment with Cytisine Doses

Of the 14 trials that have been conducted with cytisine, 10 followed a treatment schedule with 1.5 mg tablets taken orally. Participants take 6 tablets daily for 3 days before quitting smoking, dosage reduces gradually to two tablets per day over 25 days (see Table 1 above). Although this administration schedule and dosing has been efficacious, alternative schedules have been tested as a means to validate the treatment regimen. For example, the standard cytisine duration was extended with a maintenance dose of 1.5 mg twice a day from days 26 to day 84. The purpose of this dosing was to match the varenicline treatment of 12 weeks *(19)*. A second trial of extended duration tested cytisine for 6 weeks (40 days) or 12 weeks (84 days). Across two trials comparing cytisine treatment for 6 weeks versus 12 weeks (84 days), the pooled meta-analysis found that participants who received a prolonged schedule of cytisine were significantly more likely to quit smoking compared to participants who received a shorter duration of cytisine (RR = 1.29, 95% CI = 1.02-1.63; 2 trials, 1009 participants) *(18)*.

In addition to increasing the length of cytisine treatment, alternative dosing regimen of 3 mg three times daily (TID) has been studied. In this approach, the initial daily dose (9 mg) is comparable, 3 mg 3 times daily versus 1.5 mg 6 times daily. The TID schedule was introduced to ease administration and increase adherence, and to more closely match the pharmacokinetic half-life of cytisine *(9, 22)*. A 3 mg dose TID was tested in a trial of 42 or 84 days, with both resulting in significantly higher continuous smoking abstinence compared to placebo *(23)*.

Other Systematic Reviews

Several systematic reviews evaluating the studies of cytisine for tobacco cessation were identified in the evidence search but were not included. Hersi and colleagues *(24)* conducted an overview of reviews that was designed to inform the development of the Canadian Task Force on Preventive Health Care's (CTFPHC) clinical practice guideline on smoking cessation interventions in adults. Patnode and colleagues *(25)* summarized interventions for smoking cessation as an update for the US Preventive Services Task Force. Tutka and colleagues *(9)*

published a synoptic review that was a broad overview of cytisine as a medication for smoking cessation. These summaries did not add new studies to the evidence base.

Two other research teams completed systematic reviews in the same recent time frame *(26, 27)*; however, they were considered not to be the most recent.

A recent network meta-analysis (NMA) was the largest review of pharmacotherapies for smoking cessation published to date. It provides an additional perspective of cytisine contrasted with other treatment *(28)*. A network meta-analysis is a method to compare multiple treatments simultaneously in a single analysis of a network of randomized controlled trials *(29)*. In this review, Lindon and colleagues searched cumulative databases and used Cochrane methods to screen studies that used pharmacotherapies and measured treatment for 6 months or longer. The analysis involved 319 clinical trials testing all established pharmacotherapies for smoking cessation, including 7 clinical trials comparing cytisine with placebo. Across all medications, varenicline and cytisine (with high certainty) were associated with the greatest likelihood of quitting smoking at 6 months or longer (Table 5).

The hierarchy of results of the NMA when comparing smoking cessation rates at 6 months or longer, in comparison to placebo, are listed in Table 5.

Table 5. Network meta-analysis summary of findings

Component	Participants (Trials)	Relative effect RR (95% CrI)	Absolute effect Without intervention	With intervention	Certainty of the evidence
Varenicline	16,430 (67 RCTs)	OR 2.33 (2.02 to 2.68)	6 per 100	14 per 100	High
Cytisine	3848 (7 RCTs)	OR 2.21 (1.66 to 2.97)	6 per 100	13 per 100	High
Nicotine patch	37,319 (105 RCTs)	OR 1.37 (1.20 to 1.56)	6 per 100	8 per 100	High
Fast acting NRT	31,756 (120 RCTs)	OR 1.41 (1.29 to 1.55)	6 per 100	9 per 100	High
Bupropion	14,759 (71 RCTs)	OR 1.43 (1.26 to 1.62)	6 per 100	9 per 100	High

Estimates are reported as OR. Results are expressed in credibility interval (CrI) as opposed to CIs as a Bayesian analysis has been conducted.
Combination NRT was not included as a separate row, but the relative effect was calculated as OR 1.93 (1.61-2.34).

Harms

Based on decades of use as an oral medication, published reviews, and recent reports of other doses, cytisine is well tolerated as either 1.5 mg or 3 mg formulations. Overall, use of cytisine is associated with nonserious and self-limiting gastrointestinal (8%) and sleep disturbances (7%). The most recent systematic review and meta-analysis *(18)* included an assessment of harms from cytisine use in tobacco cessation. In the meta-analysis with 6 trials (Table 6), there was a slightly higher but not significant rate of adverse events in cytisine compared to placebo (RR = 1.19, 95% CI = 0.99-1.42; 6 trials 4578 participants).

Table 6. Cytisine vs Placebo Self-reported Adverse Events

	Cytisine		Comparison		RR (95% CI)
Study	Participants	Adverse Events	Participants	Adverse Events	
Dogar 2020	1239	53	1233	46	1.15 (0.77-1.70)
Nides 2021	203	102	51	28	0.92 (0.60-1.39)
Phusahat 2022	67	37	65	26	1.38 (0.84-2.28)
Rigotti 2023	539	356	270	166	1.07 (0.89-1.29)
Vinnikov 2008	85	4	86	4	1.01 (0.25-4.05)
West 2011	370	150	370	99	1.52 (1.18-1.95)
	2503	**702**	**2075**	**369**	**1.19 (0.99-1.42)**

The recent Cochrane review *(17)* assessed harms at the participant level. Across 5 studies involving 4052 participants receiving cytisine versus placebo or no medication there was a slight increase in the number of participants reporting adverse events (RR = 1.22, 95% CI = 1.07-1.39). In an additional analysis, limited to 3 studies that reported serious adverse events across 3781 participants comparing cytisine with placebo or no medication, there was no evidence of a difference in the number who experienced serious adverse events (RR = 1.04, 95% CI = 0.78 to 1.37). Study-related neuropsychiatric or cardiac serious adverse events were not reported.

Adverse Events in Cytisine versus other Medications

Only 1 trial measured adverse events comparing cytisine with NRT *(16)*. In that trial, self-reported adverse events occurred more frequently in the cytisine group compared to the NRT group (Table 7). The most common adverse events in the cytisine group were nausea and. vomiting (5%) and sleep disorders (4%). Since 2021, 3 trials have compared cytisine with varenicline *(19, 30, 31)* (Table 7). Across these trials, participant self-report of adverse events and severe adverse events occurred less frequently in the cytisine group compared to the varenicline group. When adverse event reporting was restricted to the 4th week of treatment, the effect persisted, suggesting this was not because of the shorter duration of the cytisine treatment.

Table 7. Self-reported Adverse Events in studies of Cytisine vs Varenicline or NRT

	Cytisine		Varenicline		IRR (95%CI)
Study	Participants	Adverse Events	Participants	Adverse Events	
Courtney 2021	482	997	510	1206	0.88 (0.81-0.95)
Oreskovic 2023	173	326	180	677	0.59 (0.43-0.81)
Walker 2021	111	313	138	509	0.56 (0.49-0.65)
	Cytisine		NRT		
Walker 2014	204	288	134	174	1.7 (1.4-2.0)

IRR = Incidence Rate Ratio

Summary of Benefits and Harms

Cytisine has received regulatory approval in 34 countries. Cumulatively, it is estimated that 15,000 people have participated in cytisine clinical trials worldwide. The countries participating in these trials include Australia, Bangladesh and Pakistan, Croatia and Slovenia, Germany, Italy, Kyrgyzstan, New Zealand, Poland, Russia, Thailand, and the United States. The results of the pivotal studies and those in key populations have been presented in this report.

Across 14 high-quality, randomized controlled trials, researchers have tested cytisine as a medication for smoking cessation. Based on the cumulative reviews and random effects meta-analyses, cytisine doubles the chances that people who smoke can quit smoking through 6 months or longer. Cytisine is equally as effective as varenicline, but with fewer self-reported adverse events. The most recent trials have found both longer duration of treatment and a higher dose schedule increase smoking abstinence. The balance of benefits against harms favors cytisine based on large benefits and small harms (self-limiting events and none serious).

Section 9: Summary of recommendations in current clinical guidelines

WHO Clinical Treatment Guideline

In 2024 WHO published a clinical treatment guideline for tobacco cessation in adults *(6)*. The guideline recommends with a rating of strong: varenicline, NRT, bupropion, and cytisine as pharmacological treatment options for people who smoke and want to quit. The WHO guideline recommendation for cytisine was made on the basis of the most recent systematic review and meta-analysis that was presented above *(18)*. The systematic review included 14 RCTs of cytisine: cytisine vs. placebo (8 RCTs), cytisine vs. varenicline (3 RCTs), cytisine vs. NRT (2 RCTs), and cytisine vs. behavioural counselling (1 RCT). The outcomes were long term quit rate (≥6 months) and adverse events. The results of the metal-analysis showed that participants who received cytisine were significantly more likely to quit smoking for at least 6 months than placebo/no intervention/usual care (RR=2.65, 95% CI 1.50-4.67; 6 trials, 5194 participants); significantly more likely to have higher long-term abstinence rates than participants who received NRT (RR=1.36, 95% CI 1.06-1.73, 2 trials, 1511 participants). There was no significant difference in likelihood of quitting tobacco use between cytisine and varenicline (RR=0.96, 95% CI 0.63-1.45; 3 trials, 2127). Two trials examined the impact of longer versus shorter treatment duration of cytisine, found high abstinence rates with longer treatment (RR=1.29, 95% CI 1.02-1.63; 1009 participants). While seven studies reported more AEs among those receiving cytisine compared to those who received placebo, NRT, or counselling, there was little evidence of SAEs associated with cytisine use.

The certainty of evidence for cytisine is considered moderate. This is based on several factors including the variability in dosing described in the previous sections, the modest number of countries that have approved the drug, and the absolute number of studies that have evaluated treatment in different socio-demographic groups. The guideline highlights the potential for implementation of cytisine based on large benefits, small harms, and lower cost.

United Kingdom

In February 2024, the UK National Institute for Health and Care Excellence (NICE) published an updated cytisine recommendation to be added to the existing UK tobacco guideline: Preventing uptake, promoting quitting and treating dependence *(32)*. The overall recommendation concluded that available evidence confirms cytisine has a comparable effect, safety and cost to the other recommended smoking cessation medications. The previous NICE guideline update, published in 2021, did not include cytisine as part of the evidence review because it was not fully licensed for use in the UK at the time.

Section 10. Summary of Available Data on Comparative Cost and Cost-effectiveness

Cost-effectiveness

Health technology assessment (HTA) bodies in several markets have concluded that treatment with cytisine has an acceptable cost-benefit profile as evidenced by its reimbursement status in countries across several regions including North America, Europe, Africa, the Middle East, and Asia Pacific.

West and colleagues *(15)* have argued that smoking cessation treatments are too expensive compared to the income levels of workers around the world. There is clearly a need for smoking treatments that can compete with the cost of continuing to smoke tobacco products. This is the opportunity for products like cytisine if they can be manufactured and distributed at a cost that is attractive to consumers. This is the case in Canada where cytisine is sold over the counter at about 1/5 the cost of other smoking cessation medications *(33)*.

To date, only one cost-effectiveness study has been completed involving a clinical trial of cytisine. That trial was conducted in hospitals in Bangladesh and Pakistan involving 2472 patients with newly diagnosed tuberculosis, who were provided cytisine or placebo with brief smoking cessation counseling. The trial found a very high quit rate in the placebo arm compared to cytisine (29.7% vs 32.4%)*(34)*. Patients were informed of the dangers of tobacco use on tuberculosis and they had low smoking rates per day compared to other trials. These factors likely influenced the trial quit rates. The cost utility analysis of this study found hospital costs were much higher in the cytisine arm which combined with the no treatment effect, led to the conclusion that cytisine was not cost-effective compared to placebo *(35)*.

A previous systematic review that examined studies in the Cochrane Library from December 2011 to January 2013, constructed an economic model to compare expected costs of varenicline and cytisine in the UK *(36)*. The review examined 21 trials of varenicline and 2 trials of cytisine. They concluded both treatments effective for smoking cessation but cytisine produced more quality-adjusted life-years at a lower expected cost compared to varenicline. However, this analysis was limited by the presence of only two cytisine trials and a lack of manufacturer cost data for cytisine.

In another economic analysis, researchers estimated the cost-effectiveness of making the following changes to smoking cessation services in England and the Netherlands: adding cytisine as a medication, encouraging more people who smoke to quit through brief advice, and adding support with quitting. The costs and QALYs generated by those changes over 2, 5, 10 years and a life-time were compared with that of the current practice in each country. The combined change of adding all 3 cessation services would generate an incremental net benefit of euro 11.47 (2 years) to euro 56.16 (life-time) per smoker in the Netherlands and euro 9.96 (2 years) to euro 60.72 (life-time) per smoker in England. These results suggest that smoking cessation services can benefit economically from covering cytisine and increasing behavioral support for people who smoke in both countries *(37)*.

Comparative cost

The cost of cytisine in Eastern and Central Europe is several-fold less than that of other smoking cessation medications *(9)*. Table 8 shows the cost of one course of different medications in relation to the average monthly wage in Poland *(9)*.

Table 8. Cost of One Course Treatment with Anti-smoking Agents in Relation to the Average Monthly Wage in Poland

Treatment	% of the average monthly salary
Cytisine (Tabex)	1.6
Cytisine (Desmoxan)	1.9
NRT (patches)	17.7
NRT (spray)	17.9
NRT (gum)	22.3
NRT (tablets, 4 mg)	24.6
Varenicline	24.8
Bupropion	27.3

Comparison of the international marketing data in Western European countries where cytisine, varenicline, and NRT are available shows that the cost of 12-week treatment is substantially lower for cytisine than for NRT and varenicline (see Table 9).

Table 9. Cost of 12-week Treatment with Cytisine, Varenicline, Nicotine Patch, and Nicotine Oral Spray in Average Retail Prices in Selected Western European Countries, 2024

12-week therapy	Italy	Denmark	Sweden	Spain	Portugal	UK
Varenicline (Champix)	€ 340	€ 313	€ 166	€ 279	€ 156	€ 139
Nicotine Patch (Nicorette)	€ 256	€ 310	€ 239	€ 216	€ 230	€ 215
Nicotine Spray (Nicorette)	€ 504	€ 608	€ 665	€ 570	€ 570	€ 760
Cytisine	€ 99	€ 200	€ 95	€ 112	€ 100	€ 135

Source: Analysis based on international marketing data.

Section 11: Regulatory Status, Market Availability, and Pharmacopoeial Standards

A summary listing of the active global regulatory approvals for cytisine, as of October 2024 is provided below. The regulatory status in the United Kingdom (approval in 2024) and the United States (not approved) is highlighted.

United Kingdom

In the United Kingdom, the removal of varenicline from the market in 2022 increased interest in licensing cytisine for use. The Medicines and Healthcare Products Regulatory Agency (MHRA) regulates medicines and medical devices in the UK. MHRA approved a license for cytisine in August 2023. Cytisine became available as a licensed prescription medication starting in 2024 *(38)*.

United States

In the US, cytisine has not been approved by the Food and Drug Administration (FDA) for any indication. Achieve Life Sciences, which conducted the dosing and efficacy studies of cytisinicline discussed in earlier sections, is currently pursing FDA approval for commercialization of cytisinicline for smoking cessation and nicotine dependence in the US. At the end of 2023, the US FDA expressed support for Achieve's New Drug Application (NDA) submission for cytisinicline based on adequate data to assess for efficacy from the two completed randomized controlled Phase 3 trials *(39)*. However, viewing smoking as a chronic health concern with a high risk for relapse and the need for repeat treatments, the FDA required long-term exposure data to assess for safety beyond 12 weeks. In May 2024, Achieve initiated screening for an open-label long-term exposure trial at 29 sites in the US *(40)*. Results of the trial are expected to meet the US FDA requirement to provide safety data on a minimum of 300 participants treated with cytisinicline, for smoking or nicotine vaping, for a cumulative period of 6 months and data on at least 100 participants treated for a total cumulative period of one year. Achieve anticipates submitting the NDA for cytisinicline to the US FDA in the first half of 2025.

Cytisine is mostly available in 1.5 mg tablets or film-coated tablets, in Poland also in 1.5 mg hard capsules. In specific countries, cytisine-based tobacco cessation therapies are sold in the following 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. Cytisine is sold either as prescribed medicine, or as an over the counter (OTC) product. The countries that have provided regulatory approval for cytisine for tobacco cessation are listed in Table 10.

Table 10. Country-level Cytisine Regulatory Approvals

Country	Local Trade Name	Dispensing Class
Armenia	Tabex	OTC
Austria	Asmoken	OTC
Azerbaijan	Tabex	OTC
Belgium	Decigatan	Rx
Bulgaria	Liberizin	OTC
Canada	Cravv	OTC
Czech Republic	Defumoxan, Heavis	OTC
Denmark	Decigatan	Rx
Georgia	Tabex	OTC
Germany	Asmoken,Recigar, Cytizyniclin	Rx
Greece	Tokovys	OTC
Hungary	Liberisan	Rx
Ireland	Citidaron, Tuxerdiv, Cytizinicline	Rx
Italy	Defucitan,Koayzaren, Citisiniclina	Rx
Kazakhstan	Tabex	OTC
Latvia	Tabex	OTC
Lithuania	Tabex	OTC
Malta	Novynta	Rx
Mongolia	Tabex	OTC
Netherland	Decigatan	Rx
North Macedonia	Tabex	OTC
Poland	Desmoxan, Recigar, Tabex	OTC, Rx
Portugal	Dextazin, Xistab	OTC
Romania	Defumoxan	OTC
Russian Federation	Tabex, Recigar	OTC
Serbia	Tabex	OTC
Slovakia	Defumoxan,Heavis	Rx
Spain	Todacitan, Jablerdiz, Zandraqet, Citisiniclina	Rx
Sweden	Asmoken, Cerdablan	Rx
Thailand	Cytisine	OTC
Ukraine	Tabex	OTC
United Kingdom	Cytisine, Belnifrem, Cytisinicline Adamed	Rx
Uzbekistan	Tabex, Recigar	OTC
Zambia	Cytisine	Rx

OTC: over the counter, Rx: prescription

References

1. World Health Organization. WHO report on the global tobacco epidemic, 2023: protect people from tobacco smoke. WHO; 2023 (https://www.who.int/publications/i/item/9789240077164).

2. US Department of Health and Human Services. Smoking Cessation: A Report of the Surgeon General. In. Washington (DC)2020: (Publications and Reports of the Surgeon General, https://www.ncbi.nlm.nih.gov/pubmed/32255575).

3. World Health Organization. WHO global report on trends in prevalence of tobacco use 2000–2030.2024 (https://iris.who.int/bitstream/handle/10665/375711/9789240088283-eng.pdf?sequence=1).

4. VanFrank B, Malarcher A, Cornelius ME, Schecter A, Jamal A, Tynan M. Adult Smoking Cessation - United States, 2022. MMWR Morb Mortal Wkly Rep. 2024;73(29):633-41 (https://doi.org/10.15585/mmwr.mm7329a1).

5. Hughes JR, Keely J, Naud S. Shape of the relapse curve and long-term abstinence among untreated smokers. Addiction. 2004;99(1):29-38 (https://doi.org/10.1111/j.1360-0443.2004.00540.x).

6. World Health Organization. WHO clinical treatment guideline for tobacco cessation in adults [website]. 2024 (https://www.who.int/teams/health-promotion/tobacco-control/global-tobacco-report-2023).

7. Cosmicnootropic. Tabex, 1.5mg [website]. 2024 (https://cosmicnootropic.com/wp-content/uploads/2020/05/Tabex-instruction.pdf).

8. National Center for Smoking Cessation and Training. SUMMARY OF PRODUCT CHARACTERISTICS [website]. 2024 (https://www.ncsct.co.uk/library/view/pdf/Cytisine-1-5mg-uk-spc-clean.pdf).

9. Tutka P, Vinnikov D, Courtney RJ, Benowitz NL. Cytisine for nicotine addiction treatment: a review of pharmacology, therapeutics and an update of clinical trial evidence for smoking cessation. Addiction. 2019;114(11):1951-69 (https://doi.org/10.1111/add.14721).

10. Etter JF. Cytisine for smoking cessation: a literature review and a meta-analysis. Arch Intern Med. 2006;166(15):1553-9 (https://doi.org/10.1001/archinte.166.15.1553).

11. Cahill K, Stead LF, Lancaster T. Nicotine receptor partial agonists for smoking cessation. Cochrane Database Syst Rev. 2007(1):CD006103 (https://doi.org/10.1002/14651858.CD006103.pub2).

12. Scharfenberg G, Benndorf S, Kempe G. Cytisin (Tabex) als medikamentose Raucherentwohnungshilfe. [Cytisine (Tabex) as a pharmaceutical aid in stopping smoking]. Dtsch Gesundheitsw. 1971;26(10):463-5 (https://www.ncbi.nlm.nih.gov/pubmed/4930772).

13. Cahill K, Lindson-Hawley N, Thomas KH, Fanshawe TR, Lancaster T. Nicotine receptor partial agonists for smoking cessation. Cochrane Database Syst Rev. 2016;2016(5):CD006103 (https://doi.org/10.1002/14651858.CD006103.pub7).

14. Vinnikov D, Brimkulov N, Burjubaeva A. A double-blind, randomised, placebo-controlled trial of Cytisine for smoking cessation in medium-dependent workers. J Smoking Cessation. 2008;3(1):57-62 (https://doi.org/https://doi.org/10.1375/jsc.3.1.57).

15. West R, Zatonski W, Cedzynska M, Lewandowska D, Pazik J, Aveyard P et al. Placebo-controlled trial of cytisine for smoking cessation. N Engl J Med. 2011;365(13):1193-200 (https://doi.org/10.1056/NEJMoa1102035).

16. Walker N, Howe C, Glover M, McRobbie H, Barnes J, Nosa V et al. Cytisine versus nicotine for smoking cessation. N Engl J Med. 2014;371(25):2353-62 (https://doi.org/10.1056/NEJMoa1407764).

17. Livingstone-Banks J, Fanshawe TR, Thomas KH, Theodoulou A, Hajizadeh A, Hartman L et al. Nicotine receptor partial agonists for smoking cessation. Cochrane Database Syst Rev. 2023;5(5):CD006103 (https://doi.org/10.1002/14651858.CD006103.pub8).

18. Puljevic C, Stjepanovic D, Meciar I, Kang H, Chan G, Morphett K et al. Systematic review and meta-analyses of cytisine to support tobacco cessation. Addiction. 2024;119(10):1713-25 (https://doi.org/10.1111/add.16592).

19. Walker N, Smith B, Barnes J, Verbiest M, Parag V, Pokhrel S et al. Cytisine versus varenicline for smoking cessation in New Zealand indigenous Maori: a randomized controlled trial. Addiction. 2021;116(10):2847-58 (https://doi.org/10.1111/add.15489).

20. Pastorino U, Ladisa V, Trussardo S, Sabia F, Rolli L, Valsecchi C et al. Cytisine Therapy Improved Smoking Cessation in the Randomized Screening and Multiple Intervention on Lung Epidemics Lung Cancer Screening Trial. J Thorac Oncol. 2022;17(11):1276-86 (https://doi.org/10.1016/j.jtho.2022.07.007).

21. Tindle HA, Freiberg MS, Cheng DM, Gnatienko N, Blokhina E, Yaroslavtseva T et al. Effectiveness of Varenicline and Cytisine for Alcohol Use Reduction Among People With HIV and Substance Use: A Randomized Clinical Trial. JAMA Netw Open. 2022;5(8):e2225129 (https://doi.org/10.1001/jamanetworkopen.2022.25129).

22. Nides M, Rigotti NA, Benowitz N, Clarke A, Jacobs C. A Multicenter, Double-Blind, Randomized, Placebo-Controlled Phase 2b Trial of Cytisinicline in Adult Smokers (The

ORCA-1 Trial). Nicotine Tob Res. 2021;23(10):1656-63 (https://doi.org/10.1093/ntr/ntab073).

23. Rigotti NA, Benowitz NL, Prochaska J, Leischow S, Nides M, Blumenstein B et al. Cytisinicline for Smoking Cessation: A Randomized Clinical Trial. JAMA. 2023;330(2):152-60 (https://doi.org/10.1001/jama.2023.10042).

24. Hersi M, Beck A, Hamel C, Esmaeilisaraji L, Pussegoda K, Austin B et al. Effectiveness of smoking cessation interventions among adults: an overview of systematic reviews. Syst Rev. 2024;13(1):179 (https://doi.org/10.1186/s13643-024-02570-9).

25. Patnode CD, Henderson JT, Coppola EL, Melnikow J, Durbin S, Thomas RG. Interventions for Tobacco Cessation in Adults, Including Pregnant Persons: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA. 2021;325(3):280-98 (https://doi.org/10.1001/jama.2020.23541).

26. De Santi O, Orellana M, Di Niro CA, Greco V. Evaluation of the effectiveness of cytisine for the treatment of smoking cessation: A systematic review and meta-analysis. Addiction. 2024;119(4):649-63 (https://doi.org/10.1111/add.16399).

27. Ofori S, Lu C, Olasupo OO, Dennis BB, Fairbairn N, Devereaux PJ et al. Cytisine for smoking cessation: A systematic review and meta-analysis. Drug Alcohol Depend. 2023;251:110936 (https://doi.org/10.1016/j.drugalcdep.2023.110936).

28. Lindson N, Theodoulou A, Ordonez-Mena JM, Fanshawe TR, Sutton AJ, Livingstone-Banks J et al. Pharmacological and electronic cigarette interventions for smoking cessation in adults: component network meta-analyses. Cochrane Database Syst Rev. 2023;9(9):CD015226 (https://doi.org/10.1002/14651858.CD015226.pub2).

29. Rouse B, Chaimani A, Li T. Network meta-analysis: an introduction for clinicians. Intern Emerg Med. 2017;12(1):103-11 (https://doi.org/10.1007/s11739-016-1583-7).

30. Courtney RJ, McRobbie H, Tutka P, Weaver NA, Petrie D, Mendelsohn CP et al. Effect of Cytisine vs Varenicline on Smoking Cessation: A Randomized Clinical Trial. JAMA. 2021;326(1):56-64 (https://doi.org/10.1001/jama.2021.7621).

31. Oreskovic T, Percac-Lima S, Ashburner JM, Tiljak H, Rifel J, Klemenc Ketis Z et al. Cytisine Versus Varenicline for Smoking Cessation in a Primary Care Setting: A Randomized Non-inferiority Trial. Nicotine Tob Res. 2023;25(9):1547-55 (https://doi.org/10.1093/ntr/ntad065).

32. National Institute for Health and Care Excellence (NICE). 2024 exceptional surveillance of tobacco: preventing uptake, promoting quitting and treating dependence (NICE guideline NG209). 2024.

33. Karnieg T, Wang X. Cytisine for smoking cessation. CMAJ. 2018;190(19):E596 (https://doi.org/10.1503/cmaj.171371).

34. Dogar O, Keding A, Gabe R, Marshall AM, Huque R, Barua D et al. Cytisine for smoking cessation in patients with tuberculosis: a multicentre, randomised, double-blind, placebo-controlled phase 3 trial. Lancet Glob Health. 2020;8(11):e1408-e17 (https://doi.org/10.1016/S2214-109X(20)30312-0).

35. Li J, Parrott S, Keding A, Dogar O, Gabe R, Marshall AM et al. Cost-utility of cytisine for smoking cessation over and above behavioural support in people with newly diagnosed pulmonary tuberculosis: an economic evaluation of a multicentre randomised controlled trial. BMJ Open. 2022;12(8):e049644 (https://doi.org/10.1136/bmjopen-2021-049644).

36. Leaviss J, Sullivan W, Ren S, Everson-Hock E, Stevenson M, Stevens JW et al. What is the clinical effectiveness and cost-effectiveness of cytisine compared with varenicline for smoking cessation? A systematic review and economic evaluation. Health Technol Assess. 2014;18(33):1-120 (https://doi.org/10.3310/hta18330).

37. Anraad C, Cheung KL, Hiligsmann M, Coyle K, Coyle D, Owen L et al. Assessment of cost-effective changes to the current and potential provision of smoking cessation services: an analysis based on the EQUIPTMOD. Addiction. 2018;113 Suppl 1(Suppl Suppl 1):96-105 (https://doi.org/10.1111/add.14093).

38. National Center for Smoking Cessation and Training. Cytisinicline (Cytisine) [website]. 2024 (https://www.ncsct.co.uk/publications/Cytisine-SPC).

39. Achieve Life Sciences. Achieve Life Sciences Reaches Agreement with the FDA on Long-Term Cytisinicline Exposure Data Requirements for NDA Submission [news release]. February 29, 2024.

40. Achieve Life Sciences. Achieve Life Sciences Announces Initiation of ORCA-OL Clinical Trial Evaluating Long-Term Exposure of Cytisinicline in People who Smoke or Use Nicotine E-Cigarettes [news release]. May 29, 2024.

Annex: Letters of support

Montevideo, October 29, 2024

To: WHO Expert Committee on the Selection and Use of Essential Medicines

Inclusion of cytisine on the WHO Model List of Essential Medicines (EML) for the treatment of nicotine dependence as an aid to stopping smoking and tobacco use.

From the Center for International Cooperation on Tobacco Control (CCICT) of the Ministry of Health of Uruguay -the Knowledge Hub of the WHO-FCTC focused on promoting cooperation and technical assistance in smoking cessation and treatment-, together with our recently created Nicotine Addiction and Tobacco use Treatment Initiative (NATTI) in cooperation with NextGenU.org –an online platform aimed to democratize health education globally, via free online courses- we welcome the review of cytisine on the WHO list of essential medications for tobacco cessation treatment and wish to support this inclusion.

Smoking kills more than 8 million people a year and remains a major public health problem worldwide. It kills half of its chronic users.

Quitting smoking is one of the most cost-effective actions to improve public health.

Most smokers want to quit smoking, between 40-50% try annually, but very few achieve sustained abstinence after one year when they try on their own.

This is due to the highly addictive capacity of nicotine. Nicotine dependence is an acquired, socially induced brain disease resulting from the chronic action of nicotine on the brain, and should be treated like any other chronic disease.

It has been shown that those who receive behavioral and pharmacological help significantly increase their chances of quitting smoking.

Cytisine is a plant-derived alkaloid and is the oldest drug used for smoking cessation, in Central and Eastern Europe since the mid-1960s. It has a chemical structure similar to varenicline and acts as a partial agonist of nAChRs.

The currently available evidence indicates that it has high efficacy as a smoking cessation aid (comparable to varenicline), but is cheaper. Cytisine is a safe drug, its side effects are moderate and self-limiting and less frequent than in patients using other smoking cessation drugs.

Recently, the 2024 WHO Tobacco Cessation Guidelines included cytisine as a key tool for treating tobacco use.

While Article 14 of the WHO FCTC and its implementing guidelines call on its Parties to "facilitate the accessibility and affordability of tobacco dependence treatment", the pharmacological resources available to us are scarce and not always available in all countries.

Adding cytisine to the WHO list of essential medicines has the potential to promote its inclusion in national lists, which may increase the therapeutic arsenal for treating tobacco dependence.

The CCICT of the MSP of Uruguay and NATTI are working to increase the commitment of countries, and especially of national and regional medical associations, to treat people dependent on tobacco and nicotine with evidence-based drugs, because this will save lives.

Therefore, we strongly support the inclusion of cytisine in the WHO list of essential medicines for smoking cessation for the treatment of nicotine dependence as an aid to quit smoking and tobacco use.

Kind regards,

Dr. Miguel Asqueta Sóñora
Technical Director
Center for International Cooperation on Tobacco Control
Ministerio de Salud Pública / Uruguay

SRNT
SOCIETY FOR RESEARCH ON NICOTINE & TOBACCO • 2424 American Lane • Madison, WI 53704-3102
Tel: 1-608-443-2462 Fax: 1-608-333-0310 • E-Mail: info@srnt.org • Website: http://www.srnt.org

October 28, 2024

To: WHO Expert Committee on the Selection and Use of Essential Medicines

Re: The inclusion of cytisine on the WHO Model List of Essential Medicines (EML) for the treatment of nicotine dependence as an aid to stopping smoking and tobacco use

The international Society for Research in Nicotine and Tobacco (SRNT) welcomes the opportunity to indicate its strong support for the inclusion of cytisine on the WHO's Model List of Essential Medicines (EML) for the treatment of nicotine dependence as an aid to stopping smoking and tobacco use.

Cytisine is a plant-derived alkaloid found in the so-called Golden Rain (*Laburnum anagyroides*) and other members of the *Fabaceae* family. It is one of the oldest medicines used for smoking cessation, having been available since the 1960s in Central and Eastern Europe [Tutka P, Vinnikov D, Courtney RJ, Benowitz NL. Cytisine for nicotine addiction treatment: a review of pharmacology, therapeutics and an update of clinical trial evidence for smoking cessation. *Addiction* 2019; 114: 1951-1969]. Cytisine is a partial agonist at the α4β2 subset of nicotinic acetylcholine receptors (nAChRs) that are widely distributed in the central nervous system. As a partial agonist at nAChRs, cytisine provide reduces the nicotine withdrawal symptoms that occur when an individual stops smoking. It also competitively inhibits nicotine from binding to nAChRs, thereby reducing the reward and positive reinforcement that an individual experiences when smoking a cigarette. Cytisine's mode of action is similar to that of varenicline tartrate [Formerly Champix/Chantix, now generic], the most effective smoking cessation pharmacotherapy available, although the medications have different half-lives and dosing regimens.

- Effectiveness and safety

A substantial body of evidence supports the effectiveness and safety of cytisine as a smoking cessation aid using two dosing regimens. The traditional dosing is a 25-day tapering regimen (9 mg to 1.5 mg daily. A newer higher-dose regimen of 3 mg taken 3 times daily for 6 or 12 weeks also effective and well tolerated [Rigotti NA, Benowitz NL, Prochaska J, Leischow S, Nides M, Blumenstein B, Clarke A, Cain D, Jacobs C. Cytisinicline for Smoking Cessation: A Randomized Placebo-Controlled Phase 3 Clinical Trial. JAMA 2023;330(2):152–160]. A 2023 Cochrane systematic review found cytisine to be more effective than placebo or no

medication (RR 1.30; 95% CI: 1.15-1.47; 4 trials), more effective than nicotine replacement (NRT) in one randomized trial, and similar in efficacy to varenicline but with fewer side effects [Livingstone-Banks J et al. Nicotine receptor partial agonists for smoking cessation. Cochrane Database of Systematic Reviews 2023, Issue 6. Art. No.: CD006103.]. A 2024 systematic review and meta-analysis that included several additional trials concluded that cytisine was more effective than placebo, no medication, and NRT and that it was roughly comparable to varenicline in efficacy. That analysis included an additional trial using the newer regimen reported even higher efficacy for cytisine versus placebo or no medication (RR 2.65; 95% CI: 1.50-4.67; 6 trials) [Puljevic C et al. Systematic review and meta-analysis of cytisine to support tobacco cessation. Addiction. 2024]. It also found cytisine to be more effective than nicotine replacement (RR 1.36; 95% CI: 1.06-1.73; 2 trials) and roughly comparable to varenicline (RR 0.96; 95% CI: 0.63-1.45; 3 trials). Both reviews conclude that cytisine has also demonstrated strong evidence of safety and tolerability. 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.

- Cost-effectiveness

Research has shown cytisine to have the lowest cost per quality-adjusted-life-year of all tobacco cessation medications [Stapleton J. The case for licensing cytisine now for smoking cessation is overwhelming [letter]. *BMJ* 2013; 347: f5736.], and modelling suggests cytisine may be more cost-effective than varenicline [Leaviss J, Sullivan W, Ren S, Everson-Hock E, Stevenson M, Stevens J, et al. What is the clinical effectiveness and cost-effectiveness of cytisine compared with varenicline for smoking cessation? A systematic review and economic evaluation. *Health Tech Assess* 2014; 18(33): 1-119; Anraad C, Cheung K, Hiligsmann M, Coyle K, Coyle D, Owen L, et al. Assessment of cost-effective changes to the current and potential provision of smoking cessation services: An analysis based on the EQUIPTMOD. *Addiction* 2018; Feb 11. doi: 0.1111/add.14093]. Cost-effectiveness is essential for a smoking cessation medication that needs to be globally accessible, including to governments, institutions, and individuals in low and middle-income countries. The clinical and economic characteristics of cytisine indicates that cytisine has the potential to strengthen smoking cessation efforts and increase tobacco use quit rates at global scale, but especially in low- and middle-income countries where 80% of the world's 1.3 billion tobacco users now live.

- <u>Public health impact</u>

Tobacco smoking is one of the leading causes of premature death and disease worldwide, with approximately 8 million people dying each year from smoking-related diseases. Smoking increases the risk of developing and dying from many cancers, cardiovascular disease, chronic obstructive pulmonary disease (COPD), as well as infectious diseases such as tuberculosis and HIV. Up to half of regular cigarette smokers will die of a tobacco-related disease, losing on average a decade of life expectancy. Clear evidence demonstrates that quitting tobacco use has substantial benefits, even among individuals who have smoked for decades and have developed tobacco-related chronic diseases. Smoking cessation is a key strategy endorsed by the WHO's MPOWER package against the tobacco epidemic. The WHO FCTC Article 14 and its implementation guidelines call on its Parties to "facilitate accessibility and affordability for treatment of tobacco dependence." However, the "WHO report on the global tobacco epidemic 2019: offer help to quit tobacco use" shows that cessation policies are still among the least

implemented of all WHO FCTC demand reduction measures. Adding cytisine to the WHO EML, defined as medicines to which all people should have access at all times in sufficient amounts, has the potential to act as a catalyst increase the use of smoking cessation medication globally and thereby contribute to reducing smoking prevalence and ultimately smoking related disease, disability, and death worldwide.

Based on this body of evidence, the Society for Research in Nicotine and Tobacco, the leading international research society in this field, strongly supports the inclusion of cytisine on the WHO EML for the treatment of nicotine dependence as an aid to stopping smoking and tobacco use.

Thank you for the opportunity to contribute to this important discussion.

Sincerely,

Benjamin Toll, PhD
President, SRNT
Professor and Vice Chair of Public Health
Medical University of South Carolina

ASH ACTION ON SMOKING & HEALTH

Dedicated to ZERO Tobacco Deaths

To: WHO Expert Committee on the Selection and Use of Essential Medicines

Re: The inclusion of cytisine on the WHO Model List of Essential Medicines (EML) for the treatment of nicotine dependence as an aid to stopping smoking and tobacco use

Acton on Smoking and Health welcomes the review of cytisine for inclusion on the WHO Model List of Essential Medicines (EML) for the treatment of nicotine dependence to stop nicotine addiction.

Tobacco smoking remains the leading cause of preventable death and disease worldwide and is a major global public health challenge. According to WHO estimates, there are 1.3. billion tobacco users worldwide and over 80% of them live in low- and middle-income countries. While progress has been made, the average global smoking rate remains unacceptably high and approximately 8 million people die every year from smoking related diseases.

Nicotine is a highly psychoactive substance and contributes to chronic and long-term tobacco addiction. Smoking by pregnant women increases the risk of nicotine addiction among children and may contribute to epigenetic outcomes. Smoking increases the risk of developing cancer, cardiovascular disease, chronic obstructive pulmonary disease (COPD) and many other diseases and health conditions, including infectious diseases such as tuberculosis. People who smoke and are infected by HIV or SARS-CoV-2 are at higher risk for severe disease and death compared to those who do not smoke. Cigarette smoking causes premature death. Life expectancy for people who smoke is at least 10 years shorter than for those who do not smoke. Up to two-thirds of all regular cigarette smokers will eventually die from a tobacco-related disease.

There are immediate and long-term health benefits in quitting for all tobacco users. Smoking cessation at age 50 halves the risk of premature death and cessation at age 30 reduces the risk to the level observed for people who never smoked. Ten years after quitting smoking, the risk of developing lung cancer is 50% lower compared to people who continue to smoke, and after 15 years of quitting, the risk of developing CVD is almost comparable to someone who has never smoked. There are also short-term benefits to health that occur only a few hours, weeks or months following smoking cessation, such as eliminating the exposure to such toxic chemical compounds as tobacco smoke derived carbon monoxide, reduced frequency of cough and shortness of breath, as well as improved circulation and lung function.

Global targets for tobacco use will not be reached unless current tobacco users quit. In fact, many tobacco users report that they want to quit. According to the Global Adult Tobacco

Survey (GATS), over 60% of people who smoke indicated that they intend to quit, and over 40% had attempted to quit in the past 12 months. Yet, without medications or cessation support, only about 4% of attempts to quit tobacco will succeed given the highly addictive nature of nicotine. There is an increasing consensus that tobacco dependence is a disease that must be treated by healthcare professionals through a combination of evidence-based cessation medications and behavioral counseling.

Moreover, smoking cessation is one of the main strategies suggested by the WHO's MPOWER package against the tobacco epidemic. The WHO FCTC Article 14 and its implementation guidelines call on its Parties to "facilitate accessibility and affordability for treatment of tobacco dependence". However, the "WHO report on the global tobacco epidemic 2019: offer help to quit tobacco use" shows that cessation policies are still among the least implemented of all WHO FCTC demand reduction measures, with only 23 countries in total providing best-practice cessation services, the majority of which are high income countries. There is room for greater action and adding cytisine on the WHO EML, medicines that satisfy priority healthcare needs to which people should have access at all times in sufficient amounts, has the potential to act as a catalyst for further sustainable tobacco control measures at global and national levels.

Cytisine is a plant-derived alkaloid found in the so-called Golden Rain (*Laburnum anagyroides*) and other members of the *Fabaceae* family. It is the oldest medicine for smoking cessation, used in Central and Eastern Europe since the mid-1960s. Like varenicline, that was designed from cytisine, cytisine is structurally similar to nicotine and acts as a partial agonist at nAChRs (nicotinic acetylcholine receptors), although the medications have different half-lives and dosing regimens. It effectively inhibits nicotine from binding to nAChRs and reduces the reward obtained from tobacco consumption. Results of clinical trials, systematic reviews and meta-analyses of clinical studies indicates the high efficacy of cytisine as smoking cessation aid (comparable with varenicline, evaluated to be the most effective pharmacotherapy for smoking cessation), its high cost-effectiveness (cytisine is the cheapest smoking cessation medicine, much cheaper than NRT and bupropion) and safety (adverse reactions to cytisine are moderate, non-serious, self-limiting and less frequent than in patients using other smoking cessation medicines).

As evaluated by a group of high-level experts in their statement sent to the 23rd WHO Expert Committee on the Selection and Use of Essential Medicines (see attached document), cytisine appears to be "…effective, cost-effective, safe, affordable, practicable, acceptable and equitable". The clinical and economic characteristics of cytisine indicates that this smoking cessation aid seems to be promising for strengthening smoking cessation efforts and increasing tobacco use quit rates at a global scale, but especially in low- and middle-income countries where the tobacco use epidemic and health burden from tobacco use has grown in past decades.

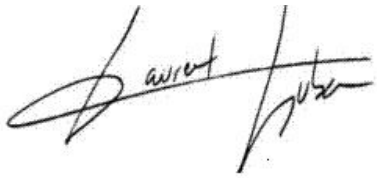
ASH
ACTION ON SMOKING & HEALTH

Dedicated to ZERO Tobacco Deaths

Action on Smoking and Health strongly believe that access to evidence-based smoking cessation medication is a key component of a comprehensive, integrated tobacco control programme. Offering tobacco users assistance in their cessation efforts will reinforce other tobacco control policies by increasing support for them and enhancing their acceptability. Effective cessation interventions save lives.

Therefore, Action on Smoking and Health strongly supports the inclusion of cytisine on the WHO EML for the treatment of nicotine dependence.

Thank you for your time and consideration,



Laurent Huber
Executive Director
Action on Smoking and Health
Washington, DC, USA

ENSP

European Network
for Smoking and Tobacco Prevention

To: WHO Expert Committee on the Selection and Use of Essential Medicines

Re: The inclusion of cytisine on the WHO Model List of Essential Medicines (EML) for the treatment of nicotine dependence as an aid to stopping smoking and tobacco use

The European Network for Smoking and Tobacco Prevention (ENSP) welcomes the review of cytisine to be included on the WHO Model List of Essential Medicines (EML) for the treatment of nicotine dependence as an aid to stopping smoking and tobacco use.

Tobacco smoking remains among the leading causes of preventable death and disease worldwide and is a major global public health challenge. According to WHO estimates, there are 1.3. billion tobacco users worldwide and over 80% of them live in low- and middle-income countries. While the smoking prevalence has been decreasing worldwide, the average global smoking rate remains unacceptably high and approximately 8 million people continue to die every year from smoking related diseases.

Nicotine is highly psychoactive substance and contributes to chronic and long-term tobacco addiction, also among teenagers. Smoking by pregnant women increases the risk of nicotine addiction among children and may contribute to epigenetic outcomes. Smoking increases the risk of developing cancer, cardiovascular disease, chronic obstructive pulmonary disease (COPD) and tens of other diseases and health conditions, including infectious diseases such as tuberculosis. Smokers infected by HIV or SARS-CoV-2 are at higher risk for severe disease and death compared to non-smokers. Cigarette smoking causes premature death. Life expectancy for smokers is at least 10 years shorter than for non-smokers. H*alf of all regular cigarette smokers will eventually be killed by their habit.*

There are immediate and long-term health benefits in quitting for all tobacco users. Smoking cessation at age 50 halves the risk of premature death and cessation at age 30 reduces the risk to the level observed for never smokers. Ten years after quitting smoking, the risk of developing lung cancer is 50% lower compared to people who continue to smoke, and after 15 years of quitting, the risk of developing CVD is almost comparable to someone who has never smoked. There are also short-term benefits to health that occur only few hours, weeks or months following smoking cessation, such as eliminating the exposure to such toxic chemical compounds as tobacco smoke derived carbon monoxide, reduced frequency of cough and shortness of breath, as well as improved circulation and lung function.

Global targets for tobacco use will not be reached unless current tobacco users quit,. In fact, many tobacco users report that they want to quit. According to the Global Adult Tobacco Survey (GATS), over 60% of smokers indicated that they intend to quit, and over 40% had attempted to quit in the past 12 months. Yet, without medications or cessation support, only about 4% of attempts to quit tobacco will succeed given highly addictive nature of nicotine. There is an increasing consensus that tobacco dependence is a disease that must be treated by healthcare professionals through a combination of evidence-based cessation medications and behavioral counseling.

Moreover, smoking cessation is one of the main strategies suggested by the WHO's MPOWER package against the tobacco epidemic. The WHO FCTC Article 14 and its implementation guidelines call on its Parties to "facilitate accessibility and affordability for treatment of tobacco dependence". However, the "WHO report on the global tobacco epidemic 2019: offer help to quit tobacco use" shows that cessation policies are still among the least implemented of all WHO FCTC demand reduction measures, with only 23 countries in total providing best-practice cessation services, the majority of which are high income countries. There is a room for greater action and adding cytisine on the WHO EML, medicines that satisfy priority healthcare needs to which people should have access at all times in sufficient amounts, has the potential to act as a catalyst for further sustainable tobacco control measures at global and national levels.

Cytisine is a plant-derived alkaloid found in the so-called Golden Rain (*Laburnum anagyroides*) and other members of the *Fabaceae* family. It is the oldest medicine used in smoking cessation, in Central and Eastern Europe since the mid-1960s. **Cytisine** is structurally similar to nicotine and acts as a partial agonist at nAChRs, and it **was a precursor for synthetic varenicline**, although the medications have different half-lives and dosing regimens. It effectively inhibits nicotine from binding to nAChRs and reduces the reward obtained from tobacco consumption. Results of clinical trials and systematic reviews and meta-analyses of clinical studies indicates on high efficacy of cytisine as smoking cessation aid (comparable with varenicline, evaluated to be the most effective pharmacotherapy for smoking cessation), its high cost-effectiveness (cytisine is the cheapest smoking cessation medicine, few times cheaper than NRT and bupropion) and safety (adverse reactions to cytisine are moderate, non-serious, self-limiting and less frequent than in patients using other smoking cessation medicines).

ENSP strongly believe that access to evidence-based smoking cessation medication is a key component of a comprehensive, integrated tobacco control programme. Offering tobacco users assistance in their cessation efforts will reinforce other tobacco control policies by increasing support for them and enhancing their acceptability. Effective cessation interventions save lives.

Therefore, ENSP strongly supports the inclusion of cytisine on the WHO EML for the treatment of nicotine dependence as an aid to stopping smoking and tobacco use.

Thank you for your time and consideration,

Prof. Florin Dumitru Mihaltan
ENSP President

Cornel Radu-Loghin
Secretary General

Brussels, 29.10.2024

RÉSEAU EUROPÉEN POUR LA PRÉVENTION DU TABAGISME aisbl

144 Chaussée d'Ixelles 1050 Brussels Belgium
T + 32 2 230 65 15 F + 32 2 230 75 07 info@ensp.org www.ensp.org

October 25th, 2024

To: WHO Expert Committee on the Selection and Use of Essential Medicines

Re: The inclusion of cytisine on the WHO Model List of Essential Medicines (EML) for the treatment of nicotine dependence as an aid to stopping smoking and tobacco use

Cancer Patients Europe (CPE) welcomes the review of cytisine to be included on the WHO Model List of Essential Medicines (EML) for the treatment of nicotine dependence as an aid to stopping smoking and tobacco use.

Tobacco smoking remains among the leading causes of preventable death and disease worldwide and is a major global public health challenge. According to WHO estimates, there are 1.3 billion tobacco users worldwide, 80% of whom live in low- and middle-income countries. Whilst smoking prevalence has been decreasing worldwide, the average global smoking rate remains unacceptably high. Approximately 8 million people continue to die every year from smoking related diseases.

Nicotine is a highly psychoactive substance and contributes to chronic and long-term tobacco addiction, even among teenagers. Smoking by pregnant women increases the risk of nicotine addiction among children and may contribute to epigenetic outcomes. It increases the risk of developing cancer, cardiovascular disease, chronic obstructive pulmonary disease (COPD) and many other diseases and health conditions, including infectious diseases such as tuberculosis. Smokers infected with HIV or SARS-CoV-2 are at a higher risk for severe disease and death compared to non-smokers. Cigarette smoking causes premature death. Life expectancy for smokers is at least 10 years shorter than for non-smokers. Half of all regular cigarette smokers will eventually be killed by their habit.

There are immediate and long-term health benefits in giving up tobacco. Smoking cessation at age 50 halves the risk of premature death and cessation at age 30 reduces the risk to the level observed for people who have never smoked. 10 years after quitting smoking, the risk of developing lung cancer is 50% lower compared to people who continue to smoke. 15 years after quitting, the risk of developing CVD is almost comparable to someone who has never smoked. There are also short-term health benefits that occur only a few hours, weeks or months following smoking cessation, for e.g. eliminating exposure to toxic chemical compounds such as carbon

Rue de l'Industrie 24
1000 Brussels, Belgium
Registration number: 0783762176
www.cancerpatientseurope.org
info@cancerpatientseurope.org

monoxide derived from tobacco, reduced frequency of coughing and shortness of breath, as well as improved circulation and lung function.

Global targets for tobacco use will not be reached unless current tobacco users quit. In fact, many tobacco users report that they want to give up. According to the Global Adult Tobacco Survey (GATS), over 60% of smokers indicated that they intend to stop smoking, and over 40% had attempted to stop in the past 12 months. Yet, without medications or cessation support, only about 4% of attempts to give up tobacco will succeed given the highly addictive nature of nicotine. There is an increasing consensus that tobacco dependence is a disease that must be treated by healthcare professionals through a combination of evidence-based cessation medications and behavioural counselling.

Moreover, smoking cessation is one of the main strategies suggested by the WHO's MPOWER package against the tobacco epidemic. The WHO FCTC Article 14 and its implementation guidelines call on its Parties to "facilitate accessibility and affordability for treatment of tobacco dependence". However, the "WHO report on the global tobacco epidemic 2019: offer help to quit tobacco use" shows that cessation policies are still among the least implemented of all WHO FCTC demand reduction measures, with only 23 countries in total providing best-practice cessation services, the majority of which are high income countries. There is room for greater action and adding cytisine to the WHO EML - medicines that satisfy priority healthcare needs to which people should have access at all times in sufficient amounts - has the potential to act as a catalyst for further sustainable tobacco control measures at national and globa levels.

Cytisine is a plant-derived alkaloid found in the so-called Golden Rain (*Laburnum anagyroides*) and other members of the *Fabaceae* family. It is the oldest medicine used in smoking cessation in Central and Eastern Europe since the mid-1960s. Like varenicline, cytisine is structurally similar to nicotine and acts as a partial agonist at Nicotinic acetylcholine receptors (nAChRs), although the medications have different half-lives and dosing regimens. It effectively inhibits nicotine from binding to nAChRs and reduces the reward obtained from tobacco consumption. Results of clinical trials and systematic reviews and meta-analyses of clinical studies indicate the high efficacy of cytisine as a smoking cessation aid (comparable with varenicline, evaluated to be the most effective pharmacotherapy for smoking cessation), its high cost-effectiveness (cytisine is the cheapest smoking cessation medicine, cheaper than NRT and bupropion) and safety (adverse reactions to cytisine are moderate, non-serious, self-limiting and less frequent than in patients using other smoking cessation medicines).

As evaluated by a group of high-level experts in their statement sent to the 23rd WHO Expert Committee on the Selection and Use of Essential Medicines (see attached

document), cytisine appears to be "…effective, cost-effective, safe, affordable, practicable, acceptable and equitable". The clinical and economic characteristics of cytisine indicate that this smoking cessation aid seems to be very promising for strengthening smoking cessation efforts and increasing tobacco use quitting rates at global scale, but especially in low- and middle-income countries where the tobacco use epidemic and health burden from tobacco use has grown in past decades.

CPE strongly believe that access to evidence-based smoking cessation medication is a key component of a comprehensive and integrated tobacco control programme. Offering tobacco users assistance in their cessation efforts will reinforce other tobacco control policies by increasing support for them and enhancing their acceptability. Effective cessation interventions save lives.

Therefore, CPE strongly supports the inclusion of cytisine on the WHO EML for the treatment of nicotine dependence as an aid to stopping smoking and tobacco use.

Thank you for your time and consideration,

DocuSigned by:
Francisco Lozano
9F89C98A2FD84D4...

Francisco Lozano
Chair of the Board

To: WHO Expert Committee on the Selection and Use of Essential Medicines

Re: The inclusion of cytisine on the WHO Model List of Essential Medicines (EML) for the treatment of nicotine dependence as an aid to stopping smoking and tobacco use

The Japan Society for Tobacco Control welcomes the review of cytisine to be included on the WHO Model List of Essential Medicines (EML) for the treatment of nicotine dependence as an aid to stopping smoking and tobacco use.

Tobacco smoking remains among the leading causes of preventable death and disease worldwide and is a major global public health challenge. According to WHO estimates, there are 1.3. billion tobacco users worldwide and over 80% of them live in low- and middle-income countries. While the smoking prevalence has been decreasing worldwide, the average global smoking rate remains unacceptably high and approximately 8 million people continue to die every year from smoking related diseases.

Nicotine is highly psychoactive substance and contributes to chronic and long-term tobacco addiction, also among teenagers. Smoking by pregnant women increases the risk of nicotine addiction among children and may contribute to epigenetic outcomes. Smoking increases the risk of developing cancer, cardiovascular disease, chronic obstructive pulmonary disease (COPD) and tens of other diseases and health conditions, including infectious diseases such as tuberculosis. Smokers infected by HIV or SARS-CoV-2 are at higher risk for severe disease and death compared to non-smokers. Cigarette smoking causes premature death. Life expectancy for smokers is at least 10 years shorter than for non-smokers. Half of all regular cigarette smokers will eventually be killed by their habit.

There are immediate and long-term health benefits in quitting for all tobacco users. Smoking cessation at age 50 halves the risk of premature death and cessation at age 30 reduces the risk to the level observed for never smokers. Ten years after quitting smoking, the risk of developing lung cancer is 50% lower compared to people who continue to smoke, and after 15 years of quitting, the risk of developing CVD is almost comparable to someone who has never smoked. There are also short-term benefits to health that occur only few hours, weeks or months following smoking cessation, such as eliminating the exposure to such toxic chemical compounds as tobacco smoke derived carbon monoxide, reduced frequency of cough and shortness of breath, as well as improved circulation and lung function.

Global targets for tobacco use will not be reached unless current tobacco users quit,. In fact, many tobacco users report that they want to quit. According to the Global Adult Tobacco Survey (GATS), over 60% of smokers indicated that they intend to quit, and over 40% had attempted to quit in the past 12 months. Yet, without medications or cessation support, only about 4% of attempts to quit tobacco will succeed given highly addictive nature of nicotine. There is an increasing consensus that tobacco dependence is a disease that must be treated by healthcare professionals through a combination of evidence-based cessation medications and behavioral counseling.

Moreover, smoking cessation is one of the main strategies suggested by the WHO's MPOWER package against the tobacco epidemic. The WHO FCTC Article 14 and its implementation guidelines call on its Parties to "facilitate accessibility and affordability for treatment of tobacco dependence". However, the "WHO report on the global tobacco epidemic 2019: offer help to quit tobacco use" shows that cessation policies are still among the least implemented of all WHO FCTC demand reduction measures, with only 23 countries in total

providing best-practice cessation services, the majority of which are high income countries. There is a room for greater action and adding cytisine on the WHO EML, medicines that satisfy priority healthcare needs to which people should have access at all times in sufficient amounts, has the potential to act as a catalyst for further sustainable tobacco control measures at global and national levels.

Cytisine is a plant-derived alkaloid found in the so-called Golden Rain (*Laburnum anagyroides*) and other members of the *Fabaceae* family. It is the oldest medicine used in smoking cessation, in Central and Eastern Europe since the mid-1960s. Like varenicline, cytisine is structurally similar to nicotine and acts as a partial agonist at nAChRs, although the medications have different half-lives and dosing regimens. It effectively inhibits nicotine from binding to nAChRs and reduces the reward obtained from tobacco consumption. Results of clinical trials and systematic reviews and meta-analyses of clinical studies indicates on high efficacy of cytisine as smoking cessation aid (comparable with varenicline, evaluated to be the most effective pharmacotherapy for smoking cessation), its high cost-effectiveness (cytisine is the cheapest smoking cessation medicine, few times cheaper than NRT and bupropion) and safety (adverse reactions to cytisine are moderate, non-serious, self-limiting and less frequent than in patients using other smoking cessation medicines).

As evaluated by group of high-level experts in their statement sent to the 23rd WHO Expert Committee on the Selection and Use of Essential Medicines (see attached document), cytisine appears to be "…effective, cost-effective, safe, affordable, practicable, acceptable and equitable". The clinical and economic characteristics of cytisine indicates that this smoking cessation aid seems to be promising for strengthening smoking cessation efforts and increasing tobacco use quit rates at global scale, but especially in low- and middle-income countries where the tobacco use epidemic and health burden from tobacco use has grown in past decades.

Japan Society for Tobacco Control strongly believe that access to evidence-based smoking cessation medication is a key component of a comprehensive, integrated tobacco control programme. Offering tobacco users assistance in their cessation efforts will reinforce other tobacco control policies by increasing support for them and enhancing their acceptability. Effective cessation interventions save lives.

Therefore, Japan Society for Tobacco Control strongly supports the inclusion of cytisine on the WHO EML for the treatment of nicotine dependence as an aid to stopping smoking and tobacco use.

Thank you for your time and consideration,

Manabu Sakuta, MD
Chairman of the Board of Directors
The Japan Society for Tobacco Control

KETCA | Kenya Tobacco Control and Health Promotion Alliance

Dereshe Towers, Suite 6.5 along Murang'a Road
P.O. Box 30958 - 00100 Nairobi, Kenya
Tel: +254 722 458 281
Email: info@ketca.org, Website: www.ketca.org

29th October 2024

To: WHO Expert Committee on the Selection and Use of Essential Medicines

Re: Proposal for the Inclusion of Cytisine in the WHO Model List of Essential Medicines (EML) for Treating Nicotine Dependence

Dear WHO Expert Committee Members,

The Kenya Tobacco Control and Health Promotion Alliance (KETCA) welcomes the review of cytisine for inclusion on the WHO Model List of Essential Medicines (EML) as a treatment for nicotine dependence and as an aid for smoking cessation. Given the critical health impacts of tobacco use in Kenya and worldwide, we believe this addition is essential for enhancing global and national tobacco control efforts.

Globally, tobacco smoking remains a leading cause of preventable disease and death. According to WHO estimates, there are over 1.3 billion tobacco users worldwide, with more than 80% residing in low- and middle-income countries like Kenya. Although smoking prevalence has shown signs of decline, the global smoking rate remains unacceptably high, leading to approximately 8 million tobacco-related deaths annually. In Kenya, tobacco-related diseases place a significant burden on our healthcare system and economy, and without expanded cessation support, these challenges will persist.

Nicotine's addictive properties are well-documented, particularly among vulnerable groups, including adolescents and pregnant women. Smoking is closely linked to an increased risk of developing cancer, cardiovascular disease, chronic obstructive pulmonary disease (COPD), and other life-threatening conditions. The need for effective cessation interventions is urgent to prevent these outcomes and protect public health.

The Value of Quitting Smoking

There are well-established benefits to quitting smoking at any age. Cessation can immediately reduce health risks and significantly lower the likelihood of tobacco-related disease. For example, quitting by age 50 halves the risk of premature death, while quitting by age 30 brings the risk profile closer to that of a non-smoker. In Kenya, over 60% of adult tobacco users express a desire to quit, yet only about 4% of those who attempt to quit without support succeed due to the addictive nature of nicotine. Evidence-based medications and behavioral support can vastly improve these quit rates.

The WHO's MPOWER strategy, along with Article 14 of the WHO FCTC, underscores the importance of providing accessible cessation resources. However, as the 2019 WHO Global Tobacco Epidemic Report illustrates, cessation services remain among the least implemented tobacco control measures, with few low- and middle-income countries offering comprehensive support. Adding cytisine to the WHO EML would strengthen cessation efforts, particularly in resource-constrained settings, enabling countries like Kenya to implement more effective, sustainable tobacco control measures.

Why Cytisine?

Cytisine, a plant-derived alkaloid found in the Golden Rain tree (Laburnum anagyroides), is a well-established smoking cessation aid, used in parts of Europe since the 1960s. It acts as a partial agonist at nicotine receptors, reducing the reward from nicotine consumption. Clinical evidence shows that cytisine is comparable to varenicline in efficacy and has high cost-effectiveness, being significantly cheaper than other cessation medications. Side effects are typically moderate and self-limiting, making it suitable for broader use, particularly in low- and middle-income countries.

Given its efficacy, affordability, and safety profile, cytisine has the potential to make cessation more accessible for millions of tobacco users. Including cytisine on the WHO EML would enhance smoking cessation efforts globally and help countries like Kenya reduce tobacco use prevalence and improve public health outcomes.

Our Recommendation

The Kenya Tobacco Control and Health Promotion Alliance strongly supports the inclusion of cytisine on the WHO EML as an essential medicine for treating nicotine dependence. Integrating cytisine into smoking cessation programs can save lives, alleviate healthcare costs, and reinforce existing tobacco control policies. By providing tobacco users with accessible and effective treatment options, we can make meaningful strides toward a healthier, tobacco-free future for Kenya and beyond.

Thank you for considering our position on this important matter.

Sincerely,

Joel Gitali

Chairman
Kenya Tobacco Control and Health Promotion Alliance

Southeast Asia Tobacco Control Alliance

28 October 2024

Expert Committee on the Selection and Use of Essential Medicines
World Health Organization
Avenue Appia 20
1211 Geneva
Switzerland

Re: cytisine in the WHO model list of essential medicines

To the **WHO Expert Committee on the Selection and Use of Essential Medicines:**

The Southeast Asia Tobacco Control Alliance (SEATCA) welcomes the upcoming review of cytisine for possible inclusion into the WHO Model List of Essential Medicines.

Smoking cessation is an important aspect of tobacco control. However, in low- to middle-income countries, there is a tendency for smoking cessation to be given a lower priority than more cost-effective population-level measures. One reason for this is the prohibitive cost of pharmacologic treatments of nicotine dependence – including bupropion, varenicline, and nicotine replacement therapy (NRT) – for low-to-middle-income countries. Furthermore, the side effect profile of antidepressants and the abuse potential of nicotine replacement therapy limit their use in real-world clinical scenarios, contributing to poor linkage to care for smoking cessation services.

Cytisine has been used in many countries and has been proven to be at least as effective as NRT and significantly less likely to produce side effects compared to antidepressants.[1] Coupled with behavioral support, cytisine's inclusion in the WHO Model List of Essential Medicines will boost smoking cessation efforts globally.

Once added to the list, official formularies of countries will follow suit, allowing this medication to be covered by social health insurance and managed care providers. In time, with widespread use, research into cytisine could drive further innovation and improve access to lifesaving medications that help with quitting tobacco products.

We urge the committee to designate cytisine as an essential medicine to be added to the WHO's model list.

Respectfully submitted,

Ulysses Dorotheo, MD, DIH, FPAO
Executive Director
ulysses@seatca.org

[1] Tinghino B, Cardellicchio S, Corso F, et al. Cytisine for smoking cessation: A 40-day treatment with an induction period. Tobacco Prevention & Cessation. 2024;10(May):23. doi:10.18332/tpc/187556.

To: WHO Expert Committee on the Selection and Use of Essential Medicines

Re: The inclusion of cytisine on the WHO Model List of Essential Medicines (EML) for the treatment of nicotine dependence as an aid to stopping smoking and tobacco use

Tobacco Free Jordan welcomes the review of cytisine to be included on the WHO Model List of Essential Medicines (EML) for the treatment of nicotine dependence as an aid to stopping smoking and tobacco use.

From a local perspective, Jordan is a LMIC with one of the highest global smoking rates among men and has an increasing prevalence of smoking amongst women. It is one of 6 countries globally where smoking prevalence is on the rise. What further complicates the picture is the high consumption of cigarettes per smoker and the diversity of products used. Tobacco and nicotine use are higher among the younger age groups than the older and the age of initiation is becoming younger.

Both the disease and economic burden from tobacco use is high in Jordan. Yearly, 9025 Jordanians lose their lives due to tobacco related deaths. In 2015, tobacco cost Jordan US$ 2.26 billion in direct and indirect health cost, bearing in mind that 60% of the county's population is 30y old and younger. According to the 2020-2022 Jordan Cancer Index, Tobacco related cancers are on the rise, and are increasing more in women than in men, reflecting high rise in women's smoking rates. This further complicates the picture, as women in childbearing age are the main consumers of tobacco and nicotine products and often face difficulties quitting before and during pregnancy, which endangers the health and life of their unborn child.

It is well known that smoking not only affects life expectancy, but also negatively affects the quality of life. With about 60% of Jordan's population being 30y old or less, along with the rising smoking rates, smoking associated diseases will increase in the coming years, with an increased health care expenditure, unless concrete steps to decrease smoking rates are taken.

Cessation is an important part of the MPOWER strategy and helps reduce smoking related morbidity and mortality rates. 45% of smokers in Jordan have tried to quit in the past 12 months. The Ministry of Health provides free cessation services, but the main medication provided are NRTs, when available. These on their own are often not sufficient due to the strong addiction. Varenicline and bupropion are not readily available, even in private sector pharmacies and are expensive for the local community. This is not a local problem, as there was a global shortage of varenicline, which affected many smokers who sought help to quit and couldn't get the necessary medications. It would also provide an option to smokers who are reluctant to use varenicline or bupropion due to various reasons.

Therefore, increasing the available options by including a well-known effective and cost-effective drug option to the WHO Model List of Essential Medicines to help smokers quit is a grave necessity and could make a tangible difference, especially in LMIC who are bearing the highest burden of tobacco related diseases and deaths globally.

Cytisine is a plant-derived alkaloid found in the so-called Golden Rain (*Laburnum anagyroides*) and other members of the *Fabaceae* family. It is the oldest medicine used in smoking cessation, in Central and Eastern Europe since the mid-1960s. Like varenicline, cytisine is structurally similar to nicotine and acts as a partial agonist at nAChRs, although the medications have different half-lives and dosing regimens. It effectively inhibits nicotine from binding to nAChRs and reduces the reward obtained from tobacco consumption. Results of clinical trials and

systematic reviews and meta-analyses of clinical studies indicates on high efficacy of cytisine as smoking cessation aid (comparable with varenicline, evaluated to be the most effective pharmacotherapy for smoking cessation), its high cost-effectiveness (cytisine is the cheapest smoking cessation medicine, few times cheaper than NRT and bupropion) and safety (adverse reactions to cytisine are moderate, non-serious, self-limiting and less frequent than in patients using other smoking cessation medicines).

As evaluated by group of high-level experts in their statement sent to the 23rd WHO Expert Committee on the Selection and Use of Essential Medicines, cytisine appears to be "…effective, cost-effective, safe, affordable, practicable, acceptable and equitable". The clinical and economic characteristics of cytisine indicates that this smoking cessation aid seems to be promising for strengthening smoking cessation efforts and increasing tobacco use quit rates at global scale, but especially in low- and middle-income countries where the tobacco use epidemic and health burden from tobacco use has grown in past decades.

Tobacco Free Jordan strongly believes that access to evidence-based smoking cessation medication is a key component of a comprehensive, integrated tobacco control program. Offering tobacco users assistance in their cessation efforts will reinforce other tobacco control policies by increasing support for them and enhancing their acceptability. Effective cessation interventions save lives.

Therefore, Tobacco Free Jordan strongly supports the inclusion of cytisine on the WHO EML for the treatment of nicotine dependence as an aid to stopping smoking and tobacco use.

Thank you for your time and consideration,

Dr Larissa Al-Uar

Founding member and Secretary General

Tobacco Free Jordan