Evidence Status Report: Cytisine for smoking cessation and reduction of nicotine cravings in smokers who are willing to stop smoking.

Report prepared by the All Wales Therapeutics and Toxicology Centre
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Key findings

Licence status
Licensed in the UK by the Medicines and Healthcare products Regulatory Agency (MHRA) in March 2019. The product was launched in the UK in January 2024. 'Cytisinicline' is used as an alternative name for cytisine in some sources.

Clinical evidence
The clinical evidence for the use of cytisine comes from a literature review conducted by AWTTC and information provided by Consilient Health Care who market one of the generic cytisine products in the UK. An exceptional surveillance report and update of NICE guideline was published in February 2024 to include cytisine as a stop-smoking intervention. Studies comparing cytisine to placebo showed superiority for cytisine (risk ratio [RR] 1.30, 95% confidence interval [CI] 1.15 to 1.47). Studies comparing cytisine to varenicline indicated comparable efficacy (RR 0.83, 95% CI 0.66 to 1.05). One study which compared cytisine to nicotine replacement therapy (NRT) showed superiority for cytisine (RR 1.43, 95% CI 1.13 to 1.80).

Safety
The clinical studies and established use of cytisine-containing products for over 50 years in the EU indicates good tolerability. The proportion of people who discontinued treatment because of adverse reactions was low and comparable to those who discontinued placebo treatment. Adverse reactions observed have usually been mild to moderate, and have most frequently concerned the gastrointestinal tract.

People factors
Tobacco is the leading single cause of premature death in Wales and a major contributor to health inequalities. Smoking-attributable mortality has decreased in Wales, however, it still accounts for over 5,000 deaths each year, around one in every six of all deaths in people aged 35 and over. Smoking is one of the main causes of inequalities in health in Wales with smoking rates higher in more deprived areas. Cytisine is another potential option in the treatment pathway for smoking cessation. It is not indicated in people under 18 years or over 65 years of age. Clinicians have stated that cytisine will likely be used by people who would have received varenicline when it was available. It is believed that this group of people are not currently receiving treatment for smoking cessation as they are not suited to nicotine replacement therapy.

Cost effectiveness
An AWTTC literature review did not identify any economic evaluations of cytisine in the target population identified by clinical experts in Wales, namely smokers who are willing to stop smoking but are unsuitable for nicotine replacement therapy or bupropion (i.e. those currently not receiving any active treatment).

An exploration of alternative comparators uncovered two economic evaluations comparing cytisine with varenicline. Both conclude that cytisine is comparatively cost-effective. However, there are notable limitations associated with these findings. A NICE exceptional review of the current evidence base concludes that cytisine has a comparable effect and safety to varenicline and is available at a relatively lower cost.

No published economic evaluations were identified comparing cytisine with NRT. However, cytisine is comparably favourable in terms of efficacy and has a lower acquisition cost.

Budget impact
AWTTC estimate that 3,868 courses will be supplied (via community pharmacy service) for cytisine in Wales annually, resulting in a net medicine acquisition cost of £444,820 and net community pharmacy fees of £179,997. However, there are uncertainties in the estimates of the number of people who may receive cytisine.

Impact on health and social care services
Introduction of cytisine is anticipated to require counselling and prescribing resource in an additional population of people who do not currently receive smoking cessation medication but who want to quit smoking. There are established smoking cessation services in Wales such as 'Help Me Quit' and Community Pharmacies supply behavioural support alongside medication. Stopping smoking is one of the biggest single interventions to improve a person's health.

Innovation and/or advantages
Cytisine offers an additional treatment option for smoking cessation and the removal of varenicline from the market in 2021 (due to safety concerns of an excipient) has led to increased interest in its use. It may be beneficial to people who are not able to tolerate, or who have not been successful with NRT.

Background

Cytisine is a plant alkaloid with a chemical structure similar to nicotine. The use of cytisine allows for a gradual reduction of nicotine dependence by relieving withdrawal symptoms. Cytisine competes with nicotine for the same receptors and gradually displaces nicotine due to its stronger binding[1]. It has been used as a smoking cessation treatment for several decades in many European countries and Canada. It is available over the counter in several countries, and it is now licensed in the UK as a prescription only medicine.

Cytisine is taken orally following a reduced dosing schedule over 25 days, however, evidence suggests that 12 weeks of treatment may be more effective[2]. This is outside the terms of the MHRA marketing approval and therefore off-label and outside the scope of AWMSG consideration. Cytisine is a new licensed medicine in the UK, approved by the MHRA as a generic based on its availability for many years in other European countries and Canada. AWTTC contacted the marketing authorisation

holders to provide a submission for appraisal by AWMSG however no submissions were received. Consilient Health who market one of the products in the UK has provided some supporting information to AWTTC.

Marketing authorisation date

Licensed in the UK by the MHRA in March 2019. Product launched in UK in January 2024.

Dosing information

Each tablet contains 1.5 mg of cytisine. One package of Cytisine (100 tablets) is sufficient for a complete treatment course. The duration of therapy is 25 days. The dosing schedule is as shown in Table 1 below[1].

Table 1. Cytisine dosing schedule[1]

Days of treatment	Recommended dosing	Maximum daily dose
From the 1st to the 3rd day	1 tablet every 2 hours	6 tablets
From the 4th to the 12th day	1 tablet every 2.5 hours	5 tablets
From the 13th to the 16th day	1 tablet every 3 hours	4 tablets
From the 17th to the 20th day	1 tablet every 5 hours	3 tablets
From the 21st to the 25th day	1-2 tablets a day	to 2 tablets

Smoking should be stopped no later than on the 5th day of treatment. In case of treatment failure, the treatment should be discontinued and may be resumed after 2 to 3 months[1].

Clinical background

Tobacco smoking is extremely damaging to health and may cause serious smoking-related illness such as cancer, heart disease, stroke, lung diseases, diabetes, and chronic obstructive pulmonary disease (COPD)[3]. It is estimated that 70% of smokers in Wales want to quit, with 4% of smokers accessing the NHS stop smoking services every year[4].

Illegal tobacco contributes to the health inequality gap in Wales due to its price and availability[4]. Twenty two percent of adults from the most deprived groups of Wales smoke, compared to 6.6% from the least deprived[4]. In 2022, the Welsh Government released a tobacco control strategy for Wales with the aim of a smoke-free Wales by 2030[5]. The strategy focuses on reducing inequalities, future generations and outlines a whole-system approach for a smoke-free Wales[5].

Incidence/prevalence

The World Health Organisation (WHO) estimates that tobacco kills more than 8 million people each year worldwide[6]. In 2021, the national average smoking prevalence was 14.1% in Wales[7]. Smoking is the leading cause of preventable morbidity and premature death in Wales. In 2018, around 5,600 deaths in people aged 35 and over were attributable to smoking[5,8]. Treating smoking-related illnesses

also has major economic impacts, costing the NHS in Wales an estimated £302 million per year[9].

Current treatment options and relevant guidance

The All Wales Medicines Strategy Group (AWMSG) endorsed an All Wales Guide: Pharmacotherapy for Smoking Cessation in February 2018[10]. The guide is currently under review and will be updated based on the outcome of consideration of this report on cytisine by AWMSG. The guide states both behavioural support and pharmacotherapies are effective in helping people to stop smoking. Combining both treatment approaches is recommended where possible. People who engage with a smoking cessation service for behavioural support to quit, should receive a supply of nicotine replacement therapy (NRT), varenicline or bupropion sufficient to last no more than two weeks after the target quit date. Phased supply should then be given after this based on suitability.

The three forms of pharmacotherapy that were licensed for use in the UK to assist with smoking cessation are:

- nicotine replacement therapy (patches, gum, lozenges, sublingual tablets, inhalator, oral spray, and nasal spray; available in range of strengths)
- bupropion (Zyban®)
- varenicline (Champix®)

These all significantly increase the chances of long-term success at stopping smoking with NRT being the most commonly used therapy. Varenicline (Champix®) is not currently available as it was withdrawn by the MHRA in 2021 as a precaution because of an impurity found in the medicine[11]. A recent update suggests the earliest it will be available again in the UK is the end of 2024[12]. Bupropion (Zyban®), is used in fewer than 1% of quit attempts in the UK[13]. Adverse events include insomnia and it is not to be used in smokers with a history of eating disorders or alcohol dependence.

The AWMSG guidance does not cover the use of electronic nicotine delivery systems (END) which include e-cigarettes and vapes as these are not MHRA licensed medicines. The AWMSG guidance is due to be updated but not before the end of 2024.

In April 2017, an integrated smoking cessation service ‘Help Me Quit’ was launched by the Welsh Government which provides evidence-based behavioural support and advice to smokers who are motivated to attempt to stop smoking[14].

The National Institute for Health and Care Excellence (NICE) published a guideline in 2021, updated in 2023: ‘Tobacco: preventing uptake, promoting quitting and treating dependence’ (NG209)[15]. In February 2024 following the Cochrane review (Livingstone-Banks et al 2023) an exceptional review to NG209 was published which focussed on cytisine as a stop-smoking intervention. The review concluded that cytisine has a comparable effect, safety and cost to the other recommended products in the guideline[16]. The National Centre for Smoking Cessation and Training (NCSCT) have also written a briefing summary and produced other resources to help practitioners prepare for helping their clients quit using cytisine[13].

Summary of evidence on clinical effectiveness

A literature search was conducted in March 2024 by the All Wales Therapeutics and Toxicology Centre (AWTTC) relating to cytisine treatment for smoking cessation and reduction of nicotine cravings in smokers willing to stop. Searches were performed using Cochrane, Central Register of Controlled Trials, EMBASE, MEDLINE and TRIP database. The primary outcome was sustained, continuous abstinence. A literature search identified 447 records which were assessed for eligibility, with 109 excluded following removal of duplicates and screening of title and abstracts. Following eligibility screening, publications deemed suitable for this report include 10 clinical trials, and two meta-analysis. The remaining records were excluded due to small numbers of people treated, incorrect cohort or unsuitable study design. Although the off-label duration of treatment is outside the scope of this review it is included as supportive evidence for efficacy and safety.

Efficacy

Livingstone-Banks et al 2023 undertook a Cochrane Review to assess the effectiveness of nicotine receptor partial agonists, including varenicline and cytisine, for smoking cessation[17]. Eight studies were included that assessed the efficacy of cytisine for smoking cessation in adults. Four studies comparing cytisine to placebo showed that cytisine helped people to quit smoking, with a moderate-certainty of evidence (risk ratio [RR] 1.30, 95% confidence interval [CI] 1.15 to 1.47). A further two studies reporting cytisine versus varenicline showed that more people in the varenicline arm quit smoking (RR 0.83, 95% CI 0.66 to 1.05). This showed a moderate-certainty of evidence, limited by the fact that the confidence intervals incorporated the potential for benefit from either cytisine or varenicline. One study compared cytisine to NRT and found that more people in the cytisine arm successfully quit than in the NRT arm (RR 1.43, 95% CI 1.13 to 1.80). The final study compared 40 days and 84 days of cytisine, and found that more people successfully quit on the longer treatment, however both durations are longer than the MHRA licensed duration of 25 days[17].

Lindson et al 2023 used the data from the Livingstone-Banks et al review to conduct a component network meta-analysis (NMA) to investigate the comparative benefits, harms and tolerability of different smoking cessation pharmacotherapies and e-cigarettes, when used to help people stop smoking tobacco[18]. Cochrane methods were used to select randomised control studies (RCTs) of smoking cessation, measured at six months or longer, using nicotine and non-nicotine e-cigarettes, cytisine, varenicline, NRT, bupropion, and nortriptyline versus no intervention, placebo or another approved pharmacotherapy. The number of RCTs included in the study was 319. The authors concluded that the most effective interventions were nicotine e-cigarettes, varenicline and cytisine (all with high-certainty). The results showed cytisine was associated with higher quit rates than control (odds ratio [OR] 2.21, 95% credibility intervals (CrI) 1.66 to 2.97; based on 7 RCTs, 3,848 participants)[18].

Randomised controlled trials

AWTTC identified 10 randomised controlled trials (RCTs) with a cytisine arm (summarised in the appendix, Table 1). Studies where the abstinence rate was measured for less than 24 weeks or where smoking cessation was not the main outcome were not included. Seven of the ten trials used the licensed regimen of cytisine consisting of 25 days of treatment. The number of participants ranged from 132 to 2,472 and trials were conducted in Kyrgyzstan, Poland, New Zealand,

Bangladesh/Pakistan, Australia, Italy, Thailand, Croatia/Slovenia and USA. Treatment was accompanied by counselling and the continuous abstinence rate was self-recorded and confirmed by carbon monoxide testing. The maximum time periods for which abstinence was recorded ranged from 24 weeks to 12 months. Five trials of cytisine were conducted versus placebo and one versus counselling alone (four of which found cytisine to be more clinically effective). Three studies of cytisine versus varenicline were found; cytisine was equally effective to varenicline in one study and less effective than varenicline in two studies. A study versus NRT showed cytisine was more effective.

Safety

Previous experience and results from clinical studies indicate a good tolerability of cytisine[1]. Cytisine has been used in Europe by several million people who smoke, and up to January 2024 there has been no evidence of any serious adverse events[13]. The proportion of people who discontinued treatment because of adverse reactions was 6 – 15.5% and in controlled studies it was comparable to the proportion of people who discontinued treatment in the placebo group[1]. The Livingstone-Banks Cochrane analysis of 3 studies showed no evidence of a difference in the number of cytisine -treated people versus those treated with placebo reporting serious adverse events (RR 1.04, 95% CI 0.78 to 1.37)[17]. Meta-analysis of two RCTs showed more people treated with varenicline versus those treated with cytisine reported serious adverse events (RR 0.67, 95% CI 0.44 to 1.03)[18].

Discussion

Cytisine is available in many countries throughout the world, including Canada and parts of Europe, where it can be bought over the counter. It has been used as a smoking cessation aid for several decades with no apparent serious side effects reported. Studies suggest cytisine is more effective than placebo or nicotine replacement therapy in achieving smoking cessation. The head-to-head comparisons between cytisine and varenicline suggest varenicline may be more effective than cytisine but side effects are less common for cytisine[19,20]. However more recent meta analyses have not found statistical differences in clinical effectiveness between the two[21,22]. Cytisine's main known side effects are gastric symptoms and sleep disturbance. The majority of adverse reactions occurred at the beginning of the therapy and resolved during treatment. Some commonly reported adverse events (e.g. irritability, weight gain, change in appetite) could also be symptoms of nicotine withdrawal associated with smoking cessation[13].

Cytisine is not recommended in people aged under 18 years, over 65 years or for pregnant and breastfeeding women. Neither is it recommended for people with unstable angina, recent myocardial infarction, clinically significant arrhythmias or who have had a recent stoke[1]. It is also cautioned for use in a number of other conditions. When reviewing the use of cytisine, NCSCT highlight these cautions and contraindications have not been updated since its original licence was granted many decades ago[13]. Clinical experts in Wales contacted by AWTTC highlight their support to ensure routine access to cytisine for people in Wales.

NRT (used by most people who obtain treatment to quit) and bupropion are the only currently available licensed pharmacotherapies for smoking cessation.
Nicotine -containing e-cigarettes (vapes) are widely available to buy in Wales. The removal of varenicline oral tablets from the market in July 2021 has led to increased

interest in the use of cytisine for smoking cessation. Clinical experts report a significant unmet need in the absence of cytisine as those people expected to benefit from its use are still smoking as there is no suitable alternative. Most of those people may previously have been eligible for treatment with varenicline and do not consider NRT appropriate for them to quit smoking. There are some differences in those eligible for treatment with cytisine compared to those formerly eligible for varenicline (as per their respective SPC's e.g. differences in contraindications).

In primary care NRT is mainly delivered by community pharmacies (a proportion of approximately 25% is also prescribed by GPs). Level 3 pharmacies provide behavioural support, supply NRT medication and conduct carbon monoxide monitoring. Level 2 pharmacies only supply NRT; with behavioural support and carbon dioxide monitoring provided by the Help Me Quit service (offered in a variety of locations including by phone). Under the community pharmacy scheme a two-week supply of pharmacotherapy is supplied initially which encourages the person to return for regular behavioural support, carbon monoxide measurement and further supply of 2 weeks of medicine, increasing the likelihood of a successful quit. Community pharmacies receive fees for providing this service up to a maximum number of eight consultations for level 3 (includes initial visit, carbon monoxide monitoring and behavioural support). Level 2 pharmacies receive fees for dispensing NRT (6 supply events during a 12 week course). Community pharmacies are reimbursed for these services and for the cost of medication supplied according to fees established in the drug tariff[23]. Cytisine is likely to be used by people who do not tolerate NRT and by people who would have received varenicline when it was available. Varenicline was primarily prescribed by GPs, however a small proportion was supplied by level 3 pharmacies. A patient group directive for supply of varenicline via community pharmacies was in development in 2021 but did not come into effect due to the cessation of supply. If cytisine is approved for use in Wales services will be updated to include this as a treatment option. Clinicans estimate that a course of cytisine will be supplied to people at 3 separate events. People receiving cytisine will be offered 12 weeks of behavioural support and carbon momoxide monitoring. Clinical experts highlight the aim for smoking cessation is to select the correct treatment the first time.

Due to the launch of cytisine in January 2024, the National Institute for Health and Care Excellence (NICE) published an exceptional review of NG209[16]. After considering the available evidence the guideline was updated to include recommendation of cytisine as an option alongside other interventions for smoking cessation. The update of the AWMSG All Wales Guide will not take place before the end of 2024.

Other benefits of cytisine highlighted are its short duration of treatment. There is potential interest in use of cytisine beyond the 25 days licensed duration of treatment, however this is outside the scope of this review and AWTTC is not aware of any plans for the licence to be reviewed.

Cost-effectiveness evidence

A literature review conducted by AWTTC did not identify any economic evaluations of cytisine for the target population: smokers who are willing to stop smoking but are unsuitable for NRT or bupropion (i.e. those currently not receiving any active treatment). However, three full economic evaluations were identified which included

cytisine as a treatment option for smoking cessation in alternative populations[24-26]. One was focused on patients with tuberculosis in Bangladesh and Pakistan, so was not directly applicable. The other two analyses potentially provide insight into the cost-effectiveness of cytisine in the UK context.

Prior to it being withdrawn from use, the targeted population would have been prescribed varenicline. Varenicline is currently recommended for use in the AWMSG All Wales Guidance for smoking cessation and is expected to be available again in the near future[10].

One of the published economic analyses used a Markov model to assess the cost-effectiveness of changes in the provision of smoking cessation programmes in England and the Netherlands[24]. Informed by published literature, analyses explored the impact of five changes to current practice, namely: the introduction of cytisine as a pharmacotherapy option, an increase in GP advice on quitting, an increase in the reach of group based behavioural therapy, an increase in the reach of SMS text-messaging services, and a combination of all of these changes. The comparator was current practice, which comprised all of the listed interventions (with relatively limited reach), including pharmacotherapy options of varenicline, NRT and bupropion. For the cytisine sub-analysis, half of all people receiving varenicline were modelled to receive cytisine instead. Applying a lifetime time horizon and an NHS perspective it was concluded that the introduction of cytisine could be a cost-effective policy change in the English population, generating a cost saving of £9.17 and a quality-adjusted life year (QALY) gain of 0.0014 per smoker (i.e. cytisine was dominant). These small differences in both costs and effects are inherently associated with a potential for instability in the cost-effectiveness estimate. An additional limitation is that this analysis was conducted using a cost for cytisine that was lower than the current price (£17.63 per treatment, price year 2015) and a cost for varenicline that was higher than the current price (£191.88 per treatment, price year 2015 (see Table 2 for current treatment costs).

A further limitation of the analysis relates to the effect estimates used in the model. They were sourced from Cochrane Reviews undertaken over a decade ago[27,28]. There is now greater uncertainty around the comparative benefit associated with cytisine. One systematic review has reported a higher odds ratio for varenicline versus control, than cytisine versus control (OR 2.33, 95% CrI 2.02 to 2.68 vs OR 2.21, 95% CrI 1.66 to 2.97), with a high level of uncertainty around the cytisine estimate[18]. Another found that the evidence for a comparison of varenicline and cytisine is limited by imprecision, concluding that the confidence intervals incorporated the potential for benefit from either cytisine or varenicline[17]. This conclusion was supported by a systematic review published in 2023 which found that cytisine was not superior to varenicline (RR 1.02, 95% CI 0.72–1.44), but was comparable with fewer adverse effects[21]. The most recent review also concluded that their analysis did not demonstrate a comparable benefit for cytisine[22].

The second economic evaluation identified by AWTTC, a National Institute for Health and Care Research (NIHR) funded economic analysis, used the Benefits of Smoking Cessation on Outcomes (BENESCO) model to assess the cost-effectiveness of standard doses of cytisine compared with varenicline, in a hypothetical cohort of 10,000 smokers, with each smoker assumed to make a single quit attempt. Although the review highlights that current services provisions include behavioural support alongside pharmacotherapy, this wasn't explicitly considered in the model. Applying a lifetime horizon and an NHS perspective, cytisine produced a QALY gain of 0.03

QALYs and a cost saving of £251 per smoker (i.e. cytisine was dominant). Cytisine was therefore identified as a cost-effective treatment option when compared with varenicline[26]. However, there are limitations to the analysis.

Notably, although the treatment cost for varenicline was equivalent to its cost when last available in the UK[29], the treatment cost for cytisine was assumed to be £16.79, which is considerably lower than its current acquisition cost. However, threshold analysis estimated that the price of the cytisine regimen would have to increase to over £250 for the total expected lifetime cost with cytisine treatment to equal the total expected lifetime cost with varenicline treatment. Currently, the cost is below that threshold (see Table 2). Secondly, the comparative efficacy was informed by a network meta-analysis (NMA) conducted in 2014 which concluded that cytisine had the highest probability of being the most effective intervention when compared with varenicline, nicotine patch and bupropion (p=0.87). However, more recent systematic reviews have concluded differently, as detailed above.

The NICE exceptional review of the current evidence base concluded that cytisine has a comparable effect and safety to varenicline and is available at a relatively lower cost[16]. Together, these conclusions suggest that cytisine could be cost-effective when compared with varenicline in smokers who are willing to stop smoking but are unsuitable for NRT or bupropion.

Although no published economic evaluations were identified comparing cytisine with NRT, one RCT found that cytisine has comparably greater clinical efficacy (RR 1.43, 95% CI 1.13 to 1.80)[30]. This efficacy benefit in favour of cytisine is supported by more recent meta-analyses[21,22]. Cytisine treatment can also be delivered at a lower cost.

Budget impact

The estimated cost of smoking cessation treatment per course per person is detailed in Table 2. Clinical experts in Wales suggest cytisine will be used for people who would otherwise have received varenicline. AWTTC sought to explore the impact of introducing cytisine for smoking cessation in Wales. Clinical experts identify a target population of smokers who wish to quit but are not suitable for NRT or bupropion. These people would have previously been prescribed varenicline. Given that varenicline has been withdrawn from use in Wales, there is no active comparative treatment included in the base case. Guided by Public Health Wales and clinical expert opinion, it is assumed that the number of people eligible to receive cytisine would be similar to the number who received varenicline (Champix®) when it was available (pre-2021), and that each person receives one course of treatment per year. Welsh primary care prescribing data reveal the largest annual cost associated with varenicline was in 2018, which was equivalent to 3,868 12-week courses. Adopting a conservative approach, it is assumed that 3,868 people would be eligible to receive cytisine, and that there would be 100% uptake. No assumptions are made about how uptake will change over time, due to the current level of uncertainty around this.

Estimated costs per course of smoking cessation therapy per person are given in Table 2 for cytisine, varenicline, NRT and bupropion. In addition to medicine acquisition costs the community pharmacy fees associated with supply of medicine, behavioural support and carbon monoxide monitoring are listed. Total fees for the

maximum number of visits were calculated from the NHS drug tariff[23] and weighted 50:50 level 2 or level 3 pharmacy, based on prescribing fee data provided by Welsh Shared Services Partnership[31]. People receiving NRT require 8 consultations for level 3 (includes initial visit, two carbon monoxide monitorings and behavioural support), and 6 medication supply visits for level 2. Experts estimate people receiving cytisine would require the same level 3 support as with NRT, but the shorter course would require fewer medication supply visits (n=3), therefore level 2 pharmacy fees would be lower.

Table 2. Estimated costs for smoking cessation treatments

Treatment	Unit cost	Example dose	Approximate medicine acquisition cost per course per person	Approximate pharmacy fee per course per person **	Approximate total cost per course per person
Cytisine*	£115 for 100 x 1.5mg tablets	100 tablets taken over 25 days	£115	£46.54	£161.54
Varenicline (Champix®)¶¶	£27.30 for 28 x 1mg tablets	168 tablets taken over 12 weeks	£163.80	£54.38	£218.18
Nicotine replacement therapy (dual therapy)†	Nicorette Invisipatch £14.72 for 14 x 25mg, £11.43 for 7 x 15mg or 10mg. Nicorette gum £23.93 for 210 x 4mg	84 patches one daily over 12 weeks; 25mg one daily for first 8 weeks, 15mg one daily for next 2 weeks and 10mg one daily for last 2 weeks. 15 gums per day over 12 weeks	£120.60 £143.58	£54.38	£318.56
Bupropion (Zyban®)††	£41.76 for 60 x 150mg tablets	120 tablets over 9 weeks of treatment	£83.52	NA	£83.52

*Cost supplied by Consilient Health[32]. PHW intend cytisine will be supplied via community pharmacies requiring the development of a patient group directive. An estimated pharmacy fee (lower than that for NRT) based on three supply events but with the same 12 week behavioural support and carbon dioxide monitoring has been calculated.
** Average of level 2 and level 3 pharmacy fees based on Wales prescribing fee data and NHS drug tariff list of fees for pharmacy services[23,31]
¶¶ Withdrawn 2021 and still currently unavailable. Varenicline was supplied by GPs but a patient group directive for supply via community pharmacies was in development in 2021 therefore a pharmacy fee for 12 weeks treatment (the same fee as used for NRT) is included for comparative purposes. Medicine acquisition cost is based on NHS Drug Tariff January 2020[29].
† Available in different product forms including patches, inhalators, gums, lozenges, sprays. NRT is mainly supplied by community pharmacies. An example cost of dual therapy using patches and gum is given with costs and estimated dosing from *Monthly Index of Medical Specialities (*MIMs)[33].
†† Bupropion is prescribed by GPs, not supplied directly by pharmacies. Cost based on *Monthly Index of Medical Specialities (*MIMs)[33].
(see AWMSG Pharmacotherapy for smoking cessation guideline, Feb 2018 for full details of dosing[10])

The results of the budget impact are presented in Table 3. AWTTC estimate that introducing cytisine would be associated with a net medicine acquisition cost of £444,820 and net community pharmacy fees (covering dispensing fee, behavioural support and carbon monoxide monitoring) of £179,997[23] (using £46.54 per person based on the average of level 2 and level 3 consultation costs). Combined the total budget impact is estimated at £624,817 per annum.

Table 3: Net budget impact for 3,868 people receiving cytisine

Comparator	Net medicine acquisition cost	Net pharmacy fees	Net budget impact
Base case			
No active comparator	£444,820	£179,997	£624,817
Scenario analyses			
varenicline	-£188,758*	-£30,344	-£219,103*
NRT	-£577,028*	-£30,344	-£607,373*
*A minus sign preceding the figure indicates a saving. No scenario has been given for bupropion as PHW, Help me Quit service and Welsh prescribing data confirm low usage in primary care. Clinicians report that routine use of bupropion is avoided due to side effects.			

The scenario analyses reveal that if varenicline is considered as the comparator treatment and all 3,868 people are assumed to receive the relatively lower cost cytisine, this would result in a total cost saving of £219,103 (assuming 100% of varenicline users complete the 12 week course). Varenicline is expected to become available again in the UK, but no earlier than the end of 2024; this scenario therefore has the potential for future plausibility.

If cytisine were to displace 12 weeks of NRT for 3,868 people the net budget impact is estimated to be a saving of £577,028 in medicine acquisition costs. The community pharmacy fees are estimated to be lower for cytisine than for NRT due to the shorter duration of the course (three versus six supply events) leading to a saving of £30,344, resulting in a total net saving of £607,373.

The budget impact analyses are associated with a number of limitations including:

- The analysis is limited to one year, which limits its scope. However, this was considered an appropriate approach due to the uncertainties around the number of people who may receive cytisine and the potential reintroduction of varenicline.
- There is notable uncertainty in the estimate of the number of people eligible. In order to estimate numbers for cytisine it was assumed that this would be the same as the maximum number of people receiving varenicline in a year which was estimated from prescribing data assuming that people received a full course of varenicline. If a large proportion of people did not complete the full 12 week course then the number of people estimated to commence cytisine will be larger. There are also some differences in those eligible for treatment with cytisine compared to those formerly eligible for varenicline (as per their respective SPC's e.g different contraindications) and the significance of this in practice in not known.
- It is assumed that only those people who are not currently receiving any active treatment will be prescribed cytisine. However, there is uncertainty around whether the wider population of people who want to quit would prefer cytisine

over NRT. If this is the case, and some of the wider population were to be prescribed cytisine, the base case does not capture this.

- The analyses are based on the licensed duration of treatment for cytisine (25 days) only. They do not explore the impact of increasing the duration of treatment which is off-label.

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Appendix 1 Summary of randomised controlled trials (RCTs) of smoking cessation (longest continuous abstinence rate period was selected)

Author/date	Treatments	Number of participants in both arms	Continuous abstinence rate: cytisine vs comparator (period)
Vinnikov 2008 (Krygystan mining community)	Cytisine licensed regimen vs placebo	171	10.6% vs 1.2%, p =0.01 (26 weeks)
West 2011 (Poland)	Cytisine licensed regimen vs placebo	1,542	8.4% vs 2.4%, p=0.001 (12 months)
Walker 2014 (New Zealand)	Cytisine licensed regimen vs nicotine replacement therapy	1,310	22% vs 15% p=0.002 (6 months)
Dogar 2020 (Bangladesh/ Pakistan patients with tuberculosis)	Cytisine licensed regimen vs placebo	2,472	32.4% vs 29.7% p=0.114 not statistically different (6 months)
Courtney 2021 (Australia)	Cytisine licensed regimen vs varenicline	1,452	11.7% vs 13.3% p = 0.03 for non -inferiority, cytisine less effective (6 months)
Walker et al 2021 (New Zealand, indiginenous Maori community)	Cytisine unlicensed regimen (12 weeks) vs varenicline	679	12.1% versus 7.9% cytisine at least as effective as varenicline (6 months)
Pastorino 2022 (Italy)	Unlicensed 40 day and 84 days cytisine vs counselling alone Counselling	869	32.1% vs 7.3% (12 months)
Phusahat 2022 (Thailand)	Cytisine licensed regimen vs placebo	132	14.93% vs 6.15% p=0.102 not statistically significant (48 weeks)
Oreskovic 2023 (Croatia/ Slovenia)	Cytisine licensed dose (25 days) vs varenicline	377	23% vs 33% cytisine less effective (24 weeks)
Rigotti et al 2023 (USA)	Unlicensed 6 week and 8-week cytisine vs placebo	810	For 6-week course: 8.9% vs 2.6% during weeks 3 to 24 (p = 0.002). For 12-week course 21.1% vs 4.8% during weeks 9 to 24 (p < 0.001).