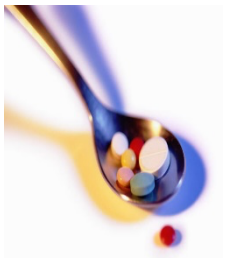

CLINICAL REFERENCE GROUP

New Medicine Request Form

Form 1

This form is to propose addition of new drugs to the formulary. Requests to amend an existing drug should be submitted on **Form 2**. Suggestions for general formulary content amendments should be submitted on **Form 3**. All forms are available at https://gmmmg.nhs.uk/joint-formulary/submissions

Please complete ALL relevant sections legibly and comprehensively. Any missing or illegible information will delay the application.

1.0 MEDICINE DETAILS:

Name of medicine (generic & proprietary name)	Cytisine
Strength(s) and form(s) of preparations of this medicine	1.5mg tablets
Licensed indication(s)	Treatment of tobacco dependency (reduction of nicotine withdrawal and cravings)
Intended indication(s) for use (if different from or in addition to the above)	As above

2.0 EVIDENCE TO SUPPORT APPLICATION

Summary of Evidence In Support Of Requested Medicine
Meta-analyses, systematic reviews, double-blind randomised controlled trials in peer reviewed journals etc. Ensure that evidence to support advantages/benefits of the new medicine over existing treatment(s) is included (if appropriate).

There is an extensive & robust evidence-base for the use of cytisine in randomised controlled trials and meta-analysis. Furthermore, a 2023 cochrane review has confirmed **cytisine to be one of the most effective treatments for tobacco dependency. It is critical patients in Greater Manchester have access to this medication.**

RCTs
1. West et al. NEJM. 2011. Increased 12-month abstinence cytisine vs placebo: RR 3.4 (1.7-7.1)
2. Walker et al. NEJM 2014. Primary outcome: continuous abstinence at 1 month increased with cytisine versus NRT (40% vs 31%, RR 1.3, 1.1-1.5, p=<0.001). Confirmed non-inferiority of cytisine versus NRT.
3. Walker et al. Addiction 2021. Primary outcome: 6-month abstinence increased with cytisine (12.1% vs 7.9%, RR 1.55, 0.97-2.46, p=<0.001). Confirmed non-inferiority of cytisine versus varenicline. Reduced adverse events with cytisine versus varenicline (RR 0.56, 0.49-0.65, p<0.001).
4. Courtney et al. JAMA 2021. Primary outcome: 6-month abstinence equivalent cytisine versus varenicline (11.7% vs 13.3%, the lower bound 97.5% CI was −5.023% for the risk difference, which extended below the lower bound of −5.0% required for noninferiority, did not reach non-inferiority). Reduced adverse events with cytisine (RR 0.88, 0.81-0.95 p=0.002)
5. Rigotti et al. JAMA 2023. Increased abstinence with cytisine versus placebo (OR 8.0, 3.9-16.3, p=<0.001)

Meta-analysis
1. Hayek et al. Thorax. 2013. Increased abstinence with cytisine vs placebo: RR 3.29 (1.84-5.90)
2. Leaviss et al. Health technology Assessment 2014. Cytisine more effective than placebo (HR 4.27, 2.05-10.05). Cytisine dominates varenicline: produces more QALYs at lower cost in 90% scenarios
3. Ofori et al. Drug and Alcohol Dependence 2023. Cytisine was superior to placebo (RR 2.25, 1.13–4.47; 5 RCTs, 4325 participants), and superior to NRT but equivalent to varenicline. Cytisine had less adverse events compared to varenicline (RR 0.67; 0.48–0.95; 3 RCTs, 2484 participants).

Cochrane review 2023
- Comprehensive study reveals nicotine e-cigarettes, varenicline and cytisine are the stop-smoking aids most likely to help people quit smoking.
- On average, for every 100 people trying to quit, around 14 are likely to succeed using an e-cigarette, varenicline or cytisine in any given quit attempt. This is compared to 6 in 100 who are likely to quit without using any aids.
- Dual nicotine replacement therapy (NRT) methods, like combining a patch with gum, may be almost as effective, with approximately 12 in 100 people likely to successfully quit. However, this estimate is less certain than those for the other stop-smoking aids.

References (please include references with written application)

RCTs

1. West et al. N Engl J Med 2011. Sep 29;365(13):1193-200. Placebo-controlled trial of cytisine for smoking cessation
2. Walker et al. N Engl J Med 2014. Dec 18;371(25):2353-62. Cytisine versus nicotine for smoking cessation
3. Walker et al. Addiction 2021. Oct;116(10):2847-2858. Cytisine versus varenicline for smoking cessation in New Zealand indigenous Māori: a randomized controlled trial
4. Courtney et al. JAMA 2021. Jul 6; 326(1): 1–10. Effect of Cytisine vs Varenicline on Smoking Cessation. A Randomized Clinical Trial
5. Rigotti et al. JAMA 2023. Jul 11;330(2):152-160. Cytisinicline for Smoking Cessation: A Randomized Clinical Trial.

Meta-analysis

1. Hayek et al. Thorax 2013. Nov;68(11):1037-42. Efficacy of cytisine in helping smokers quit: systematic review and meta-analysis
2. Leaviss et al. Health Technol Assess 2014. May; 18(33): 1–120. What is the clinical effectiveness and cost-effectiveness of cytisine compared with varenicline for smoking cessation? A systematic review and economic evaluation.
3. Ofori et al. Drug and Alcohol Dependence 2023. Volume 251, 1 October 2023, 110936. Cytisine for smoking cessation: A systematic review and meta-analysis

Cochrane review

1. Lindson et al. 2023. Cochrane Database of Systematic Reviews Review - Intervention Pharmacological and electronic cigarette interventions for smoking cessation in adults: component network meta-analyses

Provide any relevant morbidity, mortality, health economic and quality of life benefits that may be beneficial in support of this application

There is little need to state the substantial benefits that stopping smoking delivers at an individual, level, a population health level and for the health service. The substantial return on investment of treating tobacco dependency has been extensively described.

Smoking tobacco remains the single biggest cause of preventable death, disability, illness, and social inequality. At least 2 in 3 people who smoke die prematurely due to their smoking. As the leading modifiable risk factor responsible for health inequalities, smoking accounts for half the difference in life expectancy between the richest and poorest. Smoking tobacco has killed 8 million people in the UK alone in the last 50 years and without urgent action will kill another 2 million in the next 50 years. Smoking costs communities in England £17 billion a year including £2.4 billion costs to the NHS, and over £1.19 billion costs to local authorities from smoking-related social care needs.

Tobacco dependency treatment, including pharmacotherapy and specialist support, is over three times more likely to lead to long term abstinence versus no treatment. Any person that smokes must be offered access to treatment & support at every available opportunity including every touch point with the healthcare system.

Tobacco dependency in Greater Manchester

Over 5000 deaths each year in Greater Manchester (GM) are caused by smoking, with thirty times as many (currently over 150,000 people) suffering from serious smoking-related diseases in any given year. Smoking costs Greater Manchester's economy £910 million every year including:

- **£115.48 million** in NHS smoking-related healthcare
- **£62.74 million** in social care costs – people who smoke need social care at a younger age
- **£713.45 million** a year in lost earnings and employment prospects – people who smoke are more likely to become ill or die at a working age
- **£19.13** million due to smoking related fires

It's estimated that around **£681 million** is spent on tobacco and cigarettes each year in GM, equating to approximately £1,945 per person who smokes. Smoking is a driver of poverty and for most people who smoke, their addiction starts during childhood. Breaking the iron chains that have persisted between smoking and deprivation is now in sight in GM and could be delivered in less than a generation. As a city-region, our focus is on levelling up and delivering healthier places and fairer futures for all. **Tobacco has no place in that future and GM must be the first place in the UK to make history by Making Smoking History.**

A CURE Cost Benefit Analysis (CBA) indicates that the fiscal return on investment from this programme for our NHS is strong at £2.12 for every pound invested, with wider impacts on social care, businesses, poverty, and child poverty. The CBA also showed a current cost per Quality Adjusted Life Years (QALY) of £487. For reference, NICE has been using a cost effectiveness threshold of £20,000-£30,000 / QALY since 2004 in all its single technology appraisals hence NICE has concluded that that smoking cessation interventions are amongst the most cost-effective interventions that the NHS can deliver.

- **The cost per quit for the CURE Project pilot was £475 (secondary & primary care costs)**
- **The gross financial return on investment ratio was £2.12 return per £1 invested**
- **Cashable financial return on investment ratio was £1.06 return per £1 invested**
- **The public value return on investment ratio was £30.49 return per £1 invested**
- **The Incremental Cost Effectiveness Ratio (ICER) for the CURE Project pilot was £487**

This is just one example of the substantial return on investment treating tobacco dependency provides. Currently varenicline (the most effective treatment for tobacco dependency) is not available due a global recall over concerns about nitrosamine contaminants. Cytisine has been shown to be more effective than NRT and as effective varenicline with fewer side effects. It is critical that people that smoke living in Greater Manchester are provided access to this important medication to support abstinence from tobacco.

Cytisine is cheaper than combination NRT (£300 per treatment course), vaping (£150 per treatment course) and varenicline (£170 per treatment course). The short 25 day course also means this can provided in a single prescription and therefore reduces the need for repeat face to face consultations and reduces repeat prescriptions. Cytisine therefore represents a cost saving for the GM system.

Provide details of monitoring (e.g. for efficacy & adverse effects) requirements for this medicine and state if these are different from the current situation.

Cytisine is taken as 25-day course (100 tablets on a reducing regimen).
No specific monitoring is required.

Adverse events are minor, mild and significantly less than varenicline (see summary of evidence-base), the main comparator. Adverse events include increased appetite, irritability, mood changes, sleep disturbance, headaches, GI upset, dyspepsia.

3.0 FORMULARY IMPLICATIONS:

Is the medicine intended for (indicate as appropriate):

First line treatment for tobacco dependency

Which medicine(s) will this replace (if none state none)?

This may displace treatment with NRT, vaping and varenicline (once varenicline is back available in the UK – expected in the next 12 months)

Describe how the medicine compares with the existing formulary medicine(s) or treatment with regard to:

Efficacy:

More effective than NRT (see evidence base summary)
As effective as varenicline

Safety:
As with all tobacco dependency treatment – adverse effects are generally mild. However, cytisine has less adverse events than varenicline (see summary of evidence)

Tolerability & acceptability:
There are important points to raise here:

1. Cytisine is a naturally occurring plant based chemical and not a synthetic engineered chemical. This plant-based, naturally occurring nature of cytisine is highly acceptable to many people
2. The course is 25 days and can be provided in a single prescription which is highly acceptable to patients and overcomes numerous barriers to completing treatment courses for tobacco dependency

Please include guidelines for the use of the new medicine, indicating its place in the therapy of the intended indication in relation to other formulary medicines

Cytisine can be used as a first line treatment for tobacco dependency, alongside combination NRT, nicotine vapes and varenicline (the choice will be down to patient choice, previous treatments and medical history)

I would recommend GMMMG consider ab update to the Medical management of tobacco dependency guideline to include cytisine. I would be happy to support as per the first version of the guideline.

4.0 FINANCIAL AND OTHER IMPLICATIONS:

Specify number of patients requiring new medicine per annum	Estimated 500-1000 people that smoke will complete a course of cytisine per annum

Specify annual CHANGE to medicine budget expenditure:	
In Secondary Care Reduction in costs (see below)	**In Primary Care** Reduction in costs (see below)

Specify any other costs incurred by change in treatment: e.g. extra monitoring requirements	No additional costs. Cytisine costs £115 for a 25-day course but this compares to: £300 for a course of combination NRT £150 for a treatment course with nicotine vapes £170 for a treatment course with varenicline This therefore will be a cost saving by introducing cytisine to the formulary.

5.0 Red / amber / green (RAG) / grey status:

Proposed red / amber / green status (select as applicable)**:** please see guidance on defining Red, Amber Green, DNP and Grey status, available from https://gmmmg.nhs.uk/rag/rag-submissions/

Green (suitable for initiation and ongoing prescribing in primary care)	☒	**Amber (shared care).** NB: primary care will only take on shared care prescribing for patients that are stabilised on a medication and for which there is a shared care guideline	☐
Green following specialist advice	☐		
Green following specialist initiation	☐	**Red** (specialist medicines, should not be prescribed in primary care)	☐

Rationale for proposed RAG status: please comment on safety and required monitoring

Cytisine will form a central part of treating tobacco dependency protocols and could be initiated by any clinician or specialist tobacco dependency team. The efficacy of cytisine will be improved by combining with specialist support but is effective even if this is declined / not available and therefore should not have any restrictions on prescribing.

Is the medicine suitable only for exceptional use in a defined population? If so, describe the population:
NA

6.0 CONFLICTS OF INTEREST

Please declare any relevant or associated interests that may conflict with your request
e.g. funding of research, equipment, visits to conferences

Declaration of conflict of interest	Nil

For consideration at the next meeting, this form must be signed by the applicant and returned to the professional secretary of the subgroup for submission to the group two weeks (14 days) prior to the meeting. Contact details and meeting dates of the group are available on the website. Note that even if this deadline is met the group cannot guarantee that your submission will be considered at the next meeting due to existing work plans. Meetings take place every second Tuesday of each month.

Remember to enclose:

- Application Form
- Supporting Evidence
- Guidelines for Use

A copy of this completed form should also be sent to your organisations' Drug and Therapeutics Committee (D&TC) or equivalent for information.

7.0 APPLICATION FORM COMPLETED BY:

Name of applicant : ………………………………..

Job title: ……………………………………………

Department & organisation: …………………………………………..

Telephone number / email address: …………………………………

I agree to send a copy of this form to my organisations' D&TC or equivalent for information/consideration at their next meeting.

Signature: ………………………… Date: ………………….

7.0 APPLICATION FORM SUPPORTED BY:

Name of CLINICAL/MEDICAL DIRECTOR/ HEAD OF MEDICINES MANAGEMENT:

………………………………………………………………………………..

Department: ……………………………………………………………………………

Signature: ……………………………………………………………… Date: ……………………

Please send completed forms to: ……………………

For CRG Use Only

8.0 APPROVAL DECISION

Name of Medicine (generic & proprietary name)	
Requesting Consultant:	

Following a meeting of the Clinical Reference Group on the ……

The following recommendation was made:

☐ Approved as per submission
☐ Approved with the following restriction(s):

☐ Approval denied due to insufficient evidence/poor safety profile
☐ Approval denied due to negligible cost-benefit
☐ Approval deferred, request referred back for further information

This decision will be available on the GMMMG website at the following web address:
gmmmg.nhs.uk/