NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Varenicline for smoking cessation

Premeeting briefing

This briefing presents major issues arising from the manufacturer's submission (MS), evidence review group (ERG) report and statements made by consultees and their nominated clinical specialists and patient experts. Please note that although condensed summary information is included for ease of reference, this briefing should be read in conjunction with the full supporting documents.

The manufacturer was asked to provide clarification on the inclusion and exclusion criteria for trials in the base case, details about the systematic review and meta-analysis it provided, and clarification of the details and validation of the modeling.

Abbreviations

CI	95% confidence interval
ERG	evidence review group
ICER	incremental cost effectiveness ratio
MS	manufacturer's submission
NRT	nicotine replacement therapy
OR	odds ratios
QALY	quality-adjusted life year

Licensed indication

Varenicline (Champix, Pfizer) is indicated for smoking cessation in adults.

Key issues for consideration

In the manufacturer's base case analysis varenicline was more effective and less expensive than NRT and bupropion over a lifetime horizon. However, the ERG identified the following factors in the analysis that might affect cost-effectiveness estimates:

- the economic model assumed that everyone was making a single quit attempt
- extrapolating single-year trial data to a lifetime is associated with significant uncertainty
- there were computational errors in the model
- direct trial data comparing varenicline with nicotine replacement therapy (NRT) were not included in base case
- the RCTs excluded people with heart disease and diabetes mellitus (the SPC recommends that the dose of varenicline is reduced for patients with severe renal impairment).

Does the Committee consider that any one or a combination of these factors could lead to varenicline being considered not cost effective?

1 Decision problem

1.1 Decision problem approach in the manufacturer's submission

Population	Adults (over 18) who smoke tobacco products and want to quit.
Intervention	Varenicline.
Comparators	Bupropion. NRT. Placebo with/without brief advice.
Outcomes	Abstinence rates at 12 months. Health-related quality of life. Survival and smoking-related morbidity.

1.1.1 NICE guidance

'Brief interventions and referral for smoking cessation in primary care and other settings' (NICE public health intervention guidance 1) recommends that

pharmacological therapy (NRT and bupropion) should be offered only to people who have expressed a willingness to stop smoking and have either failed or refused an intensive support programme alone. Any therapy should be supported by brief advice and GP appointments.

'Guidance on the use of nicotine replacement therapy (NRT) and bupropion for smoking cessation' (NICE technology appraisal guidance 39) recommended NRT and bupropion for smokers who have expressed a desire to quit smoking. It noted insufficient evidence to recommend their use in combination. It recommended that NRT and bupropion should normally only be prescribed where a smoker has committed to stop smoking on or before a particular date. Bupropion was not recommended for smokers under 18 or pregnant women, while NRT should only be used in these groups after discussion with a relevant health care professional.

1.2 Evidence Review Group comments on the manufacturer's submission

1.2.1 Population

The ERG felt that the population was appropriate. However, no subgroups were explored such as hospitalised and preoperative patients, people with chronic obstructive pulmonary disorder and pregnant women[1].

1.2.2 Intervention

The ERG noted that the summary of product characteristics recommends that people taking varenicline should set a date to quit, and that treatment starts 1–2 weeks before this date. The dosing schedule is as follows:

[1] The summary of product characteristics states that varenicline is not recommended for use by pregnant women

Weeks	Dose	Directions
1–3	0.5mg	once daily
4–7	0.5mg	twice daily
8 to end	1mg	twice daily

Treatment should last for 12 weeks, and can be continued for an additional 12 weeks if needed. Special considerations for adverse events and dose tapering are specified in the summary of product characteristics.

1.2.3 Comparators

The ERG commented that the submission reflected currently available smoking cessation treatments used in the NHS. It noted that intensive support alone was not included in the manufacturer's submission but is an option for the NHS.

1.2.4 Outcomes

The outcomes measured were continuous abstinence rates, which were verified by an expired carbon monoxide level of 10 parts per million or less. The primary outcomes included the continuous abstinence rate in the last 4 weeks of treatment (weeks 9–12). The ERG noted that the manufacturer reported 52-week abstinence rates and that these were the main driver of the cost effectiveness analysis.

1.3 Statements from professional/patient groups and nominated experts

1.3.1 The clinical and patient specialists' were in general agreement that bupropion and NRT were the most common pharmacological therapies used in smoking cessation services in the NHS. However, they pointed out that these therapies were normally provided with counselling or behavioural support. The clinical and patient experts were also interested the potential of using varenicline in specific populations, particularly pregnant women and people who have had a myocardial infarction, and recommended further research on the use of varenicline in these groups.

2 Clinical effectiveness evidence

2.1 Clinical effectiveness in the manufacturer's submission

2.1.1 The manufacturer presented evidence from four randomised clinical trials: A3051028 (varenicline vs bupropion vs placebo; n = 1483) and A3051036 (varenicline vs bupropion vs placebo; n = 1413), were multi-centre, double-blind, randomised controlled trials. A3051035 (varenicline vs placebo; n = 2416) was a maintenance trial examining the benefit of an additional 12–weeks' treatment. A3051044 (varenicline vs NRT; n = 957) was a randomised open-label study. The manufacturer commissioned McMaster University to review smoking cessation treatments (varenicline, bupropion and NRT) and make an indirect comparison of varenicline and NRT using the placebo arms of the trials as a reference.

2.1.2 The primary endpoints were continuous abstinence rates at weeks 9–12 and weeks 13–24. The secondary endpoints were longer-term continuous abstinence rates – weeks 9–52, weeks 13–24 and from the last 4 weeks of treatment to week 52.

2.1.3 The results of the direct comparison for continuous abstinence rate for weeks 9–12 are shown in table 1. For trial A3051044 the results were analysed in two ways: using the 'intention to treat' population (all participants who were randomised regardless of whether or not they received treatment), and using the protocol pre-specified analysis, covering all participants who received at least one dose of the medication.

Table 1 Continuous abstinence rates for weeks 9–12

		n/N	Continuous quit rate % over weeks 9-12	Odds ratio (95% CI) for varenicline vs other treatment or placebo	P value for varenicline vs other treatment or placebo
A3051028	Varenicline	155/349	44.4		
	Placebo	61/344	17.7	3.85 (2.70–5.50)	< 0.001
	Bupropion	97/329	29.5	1.93 (1.40–2.68)	< 0.001
A3051036	Varenicline	151/343	43.9		
	Placebo	60/340	17.6	3.85 (2.69–5.50)	< 0.001
	Bupropion	102/340	29.8	1.90 (1.40–2.68)	< 0.001
[redacted]	[redacted]	[redacted]	[redacted]		
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]					
[redacted]	[redacted]	[redacted]	[redacted]		
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

2.1.4 The continuous abstinence rates for weeks 9–52 are shown in table 2.

Table 2 Continuous abstinence rates for weeks 9–52

		n/N	Continuous quit rate % over weeks 9-52	Odds ratio (95% CI) for varenicline vs other treatment or placebo	P value for varenicline vs other treatment or placebo
A3051028	Varenicline	155/349	21.9		
	Placebo	61/344	8.4	3.09 (1.95–-4.91)	< 0.01
	Bupropion	97/329	16.1	1.46 (0.99–2.17)	< 0.057
A3051036	Varenicline	151/343	23		
	Placebo	60/340	10.3	2.66 (1.72–4.11)	< 0.01
	Bupropion	102/340	14.6	1.77 (1.19–2.63)	0.004
[redacted]	[redacted]	[redacted]	[redacted]		
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]		
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

2.1.5 The odds ratios for the maintenance trial (A3051035) for weeks 13–24 (OR 2.47; 95% confidence interval [CI] 1.95–3.15) and weeks 13–52 (OR 1.35; CI 1.07–1.70) demonstrated statistically significant improvement in continuous abstinence rates compared with placebo.

2.1.6 The McMaster University review involved a meta-analysis of 70 NRT trials, 12 bupropion trials and four varenicline trials against control or placebo. Indirect comparison demonstrated that varenicline was superior to NRT (OR 1.66; CI 1.17–2.36) and bupropion (OR 1.78; CI 1.23–2.57). The manufacturer noted that the odds ratios were in line with the direct trials and the direction of superiority was consistent, and so concluded that varenicline was superior to NRT and bupropion.

2.1.7 The adverse events associated with varenicline treatment included nausea, flatulence and constipation, and these occurred significantly more in the varenicline groups. In the direct trials, the percentage of participants who temporarily stopped therapy because of adverse events was similar for all interventions. However, more of the participants stopped taking bupropion because of adverse events than stopped taking varenicline (15.2% vs 9.0%, A3051028 and 12.6% vs 10.5%, A3051036).

2.2 Evidence Review Group comments

2.2.1 The ERG noted a number of concerns about the clinical section of the manufacturer's submission: the inclusion and exclusion criteria of the McMaster University review; the exclusion of the direct trial of varenicline against NRT (A3051044) from the McMaster review and how the evidence was combined.

2.2.2 The ERG noted that the inclusion and exclusion criterion stated in the manufacturer's submission were different both from those used in the Cochrane reviews on smoking cessation and those used in the McMaster review. The McMaster review had included seven trials that did not chemically confirm smoking cessation and two trials that examined smoking reduction rather than cessation, although the inclusion of these trials was considered unlikely to affect the cost effectiveness. The McMaster review also included trials with different definitions of the control arm. For example, some compared to counselling alone whereas others compared to placebo. In addition, some trials investigated different types of NRT. The manufacturer excluded two placebo-controlled dose-ranging trials from their analysis. However these two studies were included in the McMaster review and therefore in the indirect comparison. The inclusion of these trials results in increasing the treatment effect of varenicline by 16% over placebo. Therefore this could make varenicline appear more effective against NRT and therefore more cost effective.

2.2.3 The ERG noted that the manufacturer excluded a number of trials that could have been included in the analysis, without giving a clear explanation of the reasoning. One of the trials excluded was an RCT that compared varenicline with placebo. The ERG speculated that this may have been excluded because the varenicline treatment duration used was 52 weeks versus the proposed 12 or 24 weeks. The ERG considered that the inclusion would have resulted in a lower ICER. Another 20 studies were excluded for reasons that the ERG considered were unclear, although for nine of these the reason may have been that they were in abstract or unpublished form. However, the ERG also noted that some studies that the manufacturer claimed to have excluded from its review were actually included.

2.3 Statements from professional/patient groups and nominated experts

2.3.1 The consensus from the clinical experts was that varenicline should ideally be given in combination with intensive support. Without this, the potential benefits of treatment might not be realised. There were comments that this type of support was offered in all the clinical trials. However, there was disagreement over whether varenicline should be provided only with intensive support. A clinical expert raised the concern that making this restriction could constrain the usage of varenicline.

3 Cost effectiveness evidence

3.1 Cost effectiveness in the manufacturer's submission

3.1.1 The manufacturer presented an economic analysis based on methods used in previous appraisals of smoking cessation. They constructed a Markov model, BENESCO (benefits of smoking cessation on outcomes), which is an update of a health-economic model developed for the World Health Organisation and used in the 'Guidance on the use of nicotine replacement therapy (NRT) and

bupropion for smoking cessation' (NICE technology appraisal guidance 39, March 2002).

3.1.2 In the BENESCO model it is assumed that patients make a single quit attempt and can be categorised into three stages: smoker, recent quitter and long-term quitter. All patients can relapse to smoker. This cohort also occupies one of nine health states which refer to the co-morbidities associated with smoking (see page 78 of MS). The transition of patients in these health states depends on what stage they are at; for example, a long-term quitter has a lower probability of dying of COPD than a current smoker. The model follows patients until they die or reach 100 years old. The model used short-term relapse rates for the interventions derived from the clinical data. However, long-term relapse rates were assumed to be independent of the smoking cessation intervention. The model takes the NHS perspective on costs and benefits.

3.1.3 The patient characteristics are taken from the Office of National Statistics figures on smoking incidence and disease incidence, and disease-specific data are from reports from organisations such as Asthma UK. Health-related utilities are derived from several published sources which use different methods of measurement. Baseline health-related utilities were adjusted to account for the age and sex of patients based on a US study. Costs are derived from NHS reference costs and published reports.

3.1.4 The efficacy rates for the comparison of varenicline with bupropion and placebo were taken from a meta-analysis of the two RCTs that included all three arms (A3051028 and A3051036). The efficacy rates for the comparison of varenicline with NRT were taken from the indirect comparison analysis. The manufacturer stated that they used the data from the indirect comparison in preference from the head-to-head trial of varenicline and NRT (A3051044) because of the higher than expected efficacy rates in that study compared with the results from the double-blind RCTs and the results from other

meta-analyses. The manufacturer included a sensitivity analysis which used the efficacy data from the head-to-head trial.

3.1.5 The results of this analysis were that, over a lifetime horizon, varenicline dominated all other treatments (that is, it was cheaper and more effective). The results of the base case are presented in Table 3 with the costs and QALY gains per person calculated by the ERG in parenthesis. These are the total costs and gains for the model population divided by the population number to give per individual gains.

Table 3 Cost effectiveness assuming a lifetime horizon

Smoking cessation intervention	Costs	QALYs	ICER
Varenicline	£34,018,920,489 (£10,717)	42,135,027 (13.27)	Dominating
Bupropion	£34,347,878,880 (£10,820)	42,063,665 (13.25)	–
NRT	£34,514,466,202 (£10,873)	42,057,446 (13.25)	–
Placebo	£34,608,281,768 (£10,903)	42,001,477 (13.23)	–

The numbers in parenthesis are the gain per person calculated by the ERG.

3.1.6 The manufacturer conducted several sensitivity analyses for varenicline examining alterations to the time horizon, the price of NRT, the health-related utility values and the age of participants. In all these analyses varenicline dominated NRT and bupropion at the lifetime horizon, and was always cost effective at the 20-year time horizon.

3.1.7 The manufacturer carried out sensitivity analysis to examine alterations in parameters. If the efficacy rates for NRT from the open-label head-to-head trial of varenicline and NRT were used, the ICER at the 10-year time horizon was approximately £7000–8000 per QALY gained and varenicline would be dominant against

NRT in the analysis using the lifetime horizon. Giving an additional 12 weeks of treatment resulted in varenicline being cost effective against placebo from the 20-year time horizon to lifetime. Other analyses included reducing the price of NRT, and varying baseline risk and utilities associated with asthma. In all these cases varenicline was cost effective over a lifetime horizon.

3.2 Evidence Review Group comments

3.2.1 The ERG recognised that the approach adopted by the manufacturer was a pragmatic one and based on previous appraisals. There were, however, a number of issues that the ERG considered could affect the cost effectiveness. These issues were:

- the assumption that participants made a single quit attempt
- long-term extrapolation
- efficacy rates,
- computational errors
- data used to populate the model.

3.2.2 The model assumed that all patients made a single quit attempt and did not try other treatments if unsuccessful. This was considered by the ERG to be unrealistic and could potentially limit the external validity of the model. The ERG was unable to predict how this would affect the cost effectiveness. The ERG also questioned the assumption of extrapolating the benefits of the trials to a lifetime horizon and considered that since the relapse rates are assumed to be the same for all treatments (see figure 5 in the ERG report), the treatment with the highest 1-year abstinence rates will be cost effective as long as the costs are not markedly high. This uncertainty over the long-term efficacy of the interventions could have considerable impact on the cost effectiveness estimates when estimated over shorter time horizons.

3.2.3 The ERG was concerned that the manufacturer calculated efficacy rates from pooling the 1-year abstinence rates, since there is no acknowledged methodology to calculate rates from odds ratios. The manufacturer claimed it was appropriate to pool given the similarity in the trial designs and results. The ERG considered that a model constructed around odds ratios would have been preferable. In addition the odds ratios were estimated from the McMaster review, which the ERG noted 'creates an optimistic basis for the indirect comparison of varenicline with NRT'. The effect of this on the cost effectiveness was unknown to the ERG. However, the manufacturer's approach was similar to that from an HTA report by Woolacott and colleagues, which was used in 'Guidance on the use of nicotine replacement therapy (NRT) and bupropion for smoking cessation' (NICE technology appraisal guidance 39, March 2002).

3.2.4 The ERG considered that the open-label trial comparing varenicline to NRT (A3051044) should have been included in the manufacturer's original submission because the lack of blinding would be assumed to affect the control arm rather than the intervention arm. In addition, the NICE technology appraisal methods guide states that direct head-to-head data should take precedence over indirect analysis. However, the direct data from this trial does support the results of the indirect analysis.

3.2.5 The data used to populate the model was questioned by the ERG, particularly the US data on long-term abstinence rates and relative risks or morbidity and mortality. It was unclear to the ERG how applicable US data was to the UK population and whether this would affect the external validity of the model. In addition, the method used to select studies to inform the model parameters was not described.

3.2.6 The ERG identified a number of computational errors in the model. The ERG noted that the model did not comply with one of the

underlying principles of transition state transition models, that each patient should be categorised into one health state at any given time point over the duration of the model. Moreover, the population in the model increased between year 0 and year 1. It then decreases over the subsequent years. The manufacturer disputed that this was an error in the model and argued that the number of patients remained the same throughout the duration of the model. The ERG also noted an error in the way in which the probability of death for people without smoking-related morbidities were estimated. However, it concluded that this would bias against more effective smoking cessation interventions. It also noted an error in the relapse probabilities used, but concluded that the effect would be minor.

3.2.7 The ERG noted from the probabilistic sensitivity analysis that the comparative degree of uncertainty was greater for varenicline versus placebo, than for bupropion and NRT versus placebo. When compared marginally against placebo alone, varenicline, bupropion and NRT are expected to dominate placebo. The ERG considered that this is likely to be largely due to the use of independent efficacy rates from the clinical trials instead of modelling the relative efficacy of the interventions against placebo using odds ratios or relative risks.

3.2.8 The ERG attempted to validate the model by comparing it with previous assessments of smoking cessation. The ERG compared the BENESCO model with two other analyses that were produced for 'Guidance on the use of nicotine replacement therapy (NRT) and bupropion for smoking cessation' (NICE technology appraisal guidance 39)' – a published simulation model [PREVENT] and an analysis based on a 40-year cohort study of British male doctors by Doll and colleagues. The long-term assumptions on life years saved in the manufacturer's model seem to be within reasonable limits in comparison with the simulation model. However, the

assumptions employed within the model seem to be conservative in comparison with the Doll analyses.

3.3 ERG sensitivity analysis

3.3.1 The ERG re-ran the systematic review and meta-analysis of smoking cessation trials using their own inclusion and exclusion criteria. This estimated the effectiveness of NRT as 82% greater than using placebo (OR 1.82; CI 1.60–2.08), which is 11% higher than that reported in the McMaster review. The ERG's estimate for bupropion against placebo was 26% greater than that reported in the McMaster University review. The ERG then carried out their own indirect comparison of varenicline and NRT using methods described by Bucher, and this showed that varenicline was superior to NRT when compared to a placebo control at 1 year (OR 1.54; CI 1.10–2.16; P = 0.01) This is 12% lower than the estimate derived from McMaster indirect comparison and [redacted]

4 Authors

Prashanth Kandaswamy and Louise Longworth, on behalf of the Committee Chair (Andrew Stevens) and the Lead Team (Mike Campbell and Catherine Patricia Thomas).