

varenicline 1mg tablets (Champix®)
Pfizer Ltd

No. (336/06)

8 December 2006

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

varenicline tablets (Champix®) is accepted for use within NHS Scotland for smoking cessation in adults. It should be used only as a component of a smoking cessation support programme. The benefits of an additional treatment course in those who have stopped smoking after the initial 12 weeks of therapy appear modest.

Efficacy and safety in patients with significant co-morbidity are uncertain.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Indication

Smoking cessation in adults.

Dosing information

0.5mg daily on days 1-3, 0.5mg twice daily on days 4-7 and 1mg twice daily thereafter for 12 weeks. For patients who have successfully stopped smoking at 12 weeks, an additional 12 week treatment course may be considered.

Date of licensing or licence status on date of review

Approved by the European Medicines Control Agency (EMA) September 2006

Product availability date

November 2006

Summary of evidence on comparative efficacy

Varenicline is a selective nicotinic acetylcholine receptor partial agonist that binds specifically to the $\alpha 4\beta 2$ nicotinic receptor subtype. This receptor modulates the release of dopamine in response to nicotine, reinforcing its rewarding properties. Varenicline releases less dopamine, and releases it more slowly, than nicotine; theoretically this should reduce the craving and withdrawal symptoms of smoking cessation without producing its own dependence syndrome. Varenicline has a greater affinity than nicotine for the $\alpha 4\beta 2$ nicotinic receptor and therefore also acts as a competitive antagonist.

There have been three pivotal, phase III studies in healthy smokers. Two of the phase III studies were of the same design while the third looked at extended treatment with varenicline. The two comparative, double-blind, placebo- and active-controlled, phase III studies randomised a total of 2045 patients in a 1:1:1 ratio to varenicline 1mg twice daily (n=692), bupropion SR 150mg twice daily (n=669) or placebo (n=684) for 12 weeks then followed the patients for 40 weeks post treatment. Patients were aged 18-75 years and had to be motivated to stop smoking, have smoked an average ≥ 10 cigarettes per day over the previous year with no periods of abstinence >3 months and have had no serious or unstable disease in the previous six months. Patients were given a self-help guide to smoking cessation and attended weekly clinics during the 12 weeks of treatment when individual counselling for up to ten minutes was provided. The primary outcome was the exhaled carbon monoxide (CO)-confirmed four-week continuous quit rate (CQR) for weeks 9-12. Patients who reported complete abstinence from smoking for the last four weeks of treatment, with end-expiratory exhaled CO measurements ≤ 10 parts per million were classed as responders. Secondary outcome measures included continuous abstinence rate (CAR) from week nine through to week 52, Minnesota Nicotine Withdrawal Scale (MNWS) and change in body weight.

For both studies the percentage of patients achieving a CQR was significantly greater in the varenicline arms (44%) compared with bupropion arms (30%, $p < 0.001$) and with placebo (18%, $p < 0.001$). Significantly more patients in the varenicline than in the placebo groups were continuously abstinent at week 52 (22% vs 8.4%, $p < 0.001$ and 23% vs 10.3%, $p < 0.001$). However, this difference was only significant compared with bupropion in study two (22% vs 16%, $p = 0.057$ and 23% vs 15%, $p = 0.004$).

In assessments on the MNWS both varenicline and bupropion significantly reduced the urge to smoke and the negative affect compared with placebo. Mean weight gain was greater for varenicline patients than placebo patients and was greater in those who maintained abstinence than those who were smokers. A greater proportion of patients in the abstinent group had a weight gain $\geq 3\%$ than in the smokers group (60-73% vs 30-41%), but within the abstinent population the proportion with a weight gain of $\geq 3\%$ was less in the varenicline group than the placebo group (60% vs 72% and 70% vs 73% for both studies). Mean weight gain was lower in all bupropion groups.

The third study included 1927 smokers and the aim was to determine if an additional 12 weeks of varenicline treatment would maintain abstinence and prevent relapse. There were three phases; an initial 12-week open-label treatment with varenicline 1mg twice daily after which patients who had abstained from smoking and nicotine replacement therapy (NRT) for at least the last seven days were randomised to double-blind treatment with either continued varenicline (n=602) or placebo (n=604) for 12 weeks and then followed for 28 weeks post-treatment. Inclusion and exclusion criteria and counselling were as previously described. The primary outcome was the CAR assessed at week 13 through to week 24, with the key secondary measure, CAR week 13 through to 52. At week 24, the CAR was significantly higher in the varenicline arm than with placebo (71% vs 50%, $p < 0.001$) and patients were more than twice as likely to have remained abstinent (OR 2.48 (95% CI: 1.95-3.16)). At week 52, the difference was still significant but the gap between treatments had reduced (44% vs 37%, OR 1.34 (95% CI: 1.06-1.69), $p < 0.02$). Mean weight gain in responders was less in the varenicline arm than with placebo (0.8kg vs 1.5kg).

Summary of evidence on comparative safety

Overall rates of all-causality adverse events were similar across all groups, with treatment related adverse events higher in the two active treatment groups. In the varenicline group in the two comparative studies with bupropion, the most frequent adverse events were nausea (28% vs 12% and 29% vs 7% for varenicline vs bupropion, respectively), insomnia (14% vs 22% and 14% vs 21%), abnormal dreams (10% vs 5% and 13% vs 6%) and headache (15% vs 14% and 13% vs 8%). Safety data are not available for people with significant co-morbidities as these patients were excluded from the studies.

*Other data were also assessed but remain commercially confidential.**

Summary of clinical effectiveness issues

The Scottish legislation banning smoking from all enclosed public places and the many government policy documents on smoking cessation indicate the determination to reduce the number of smokers and the associated burden of death and disease in Scotland. All Scottish health boards have smoking cessation programmes in place offering support and the supply of NRT and bupropion to patients wishing to quit.

Varenicline is a non-nicotine smoking cessation agent which has demonstrated a higher CAR at 12 weeks and one year than either bupropion or placebo. However, there are as yet no published comparative studies against NRT, the most commonly used pharmacological aid, although a large ongoing study should report by the end of 2006. There are a number of factors in the varenicline studies that might affect their generalisability to the Scottish population. Both of the comparative studies with bupropion were conducted solely in the USA and this is reflected in the 12 weeks of bupropion therapy rather than the 7-9 weeks recommended in the UK. Patients were recruited at academic medical centres and this may account for the high response rates, including placebo response, reported in these studies.

Smoking prevalence in Scotland in men and women is less than 20% in the top socio-economic quintile and over 40% in the bottom quintile, the most deprived group. This is the group most likely to present with the co-morbidities (severe cardiovascular disease, uncontrolled hypertension, chronic obstructive pulmonary disease, a history of cancer, current or recent depression) that were excluded from the clinical studies. The clinical study populations are therefore unlikely to be representative of the Scottish population seeking treatment.

In the study of extended treatment with varenicline only those patients who responded to 12 weeks of open-label therapy were randomised to the double-blind phase and this may have biased the outcomes. Further analysis by the Food and Drug Administration did confirm that 24 weeks of varenicline provided better abstinence rates than 12 weeks after all patients were followed for the same length of time post-treatment. Both groups show that the first three months after treatment discontinuation are vulnerable to relapse, however, the relapse curve for those who had a longer period of varenicline treatment was shallower. Nevertheless the overall benefits of the additional 12 week treatment course appear modest.

There was a high level of support given to patients in the studies and this may have influenced discontinuation rates due to adverse events as well as abstinence rates. Support networks are available through the smoking cessation programmes in Scotland. The company will provide a telephone support programme as an adjunct to currently available smoking cessation services. Many disparate factors affect success in stopping smoking. These can include social factors; where, how, who and for how long an intervention takes place; but the most important factor is the commitment and the will to quit as at present, regardless of the intervention, the majority of smokers fail to stay abstinent at one year.

Summary of comparative health economic evidence

The manufacturer submitted a cost-utility analysis based on an existing Markov model. Clinical data were taken from randomised trials of varenicline and bupropion, combined with indirect comparisons with NRT and counselling. Treatment duration was 12 weeks of varenicline, 10 weeks of NRT, and 7 weeks of bupropion. Costs of diseases avoided as a result of quitting were estimated using longitudinal epidemiological data plus English NHS cost sources. Under baseline assumptions, varenicline dominates i.e. compared to other ways of quitting smoking it results in lower total lifetime NHS costs for a cohort of smokers while yielding the most QALYs.

The model chosen had previously been reviewed by NICE in an HTA and judged appropriate. Clinical efficacy data were drawn from head-to-head RCTs or from well-designed meta analyses. Health benefits were measured in QALYs and conservative assumptions were used in their calculation, slanting the analysis against varenicline.

Some aspects of the way treatment cost-savings were calculated are open to challenge such as assuming an incident case of smoking-related disease would lead to a hospital admission – this may be true for lung cancer or stroke but is less appropriate for COPD. However, the range of smoking-related diseases considered was quite limited, which is a conservative assumption, and the sensitivity analysis shows the results are not affected by these savings. Indeed when the cost savings were reduced to £1 the cost/QALY increased to less than £1000 compared to NRT. The manufacturer also estimated that the cost/QALY comparing 12 weeks of varenicline with 24 weeks would be £245.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

There have been seven government policy documents to reduce the number of smokers and the associated burden of death and disease in Scotland since 1998, culminating in the Smoking, Health and Social Care (Scotland) Act, 2005 which banned smoking in enclosed public places.

In 2000, the former Health Education Board for Scotland and Action on Smoking and Health (ASH) Scotland published Smoking Cessation Guidelines for Scotland with an update in 2004 from Health Scotland and ASH Scotland. August 2001, NHS circular: HDL (2001) to all Health Boards in Scotland provided guidance and funding for the establishment of smoking cessation programmes.

In March 2002, National Institute of Health and Clinical Excellence (NICE) issued Technology Appraisal Guidance no.39. Guidance on the use of nicotine replacement therapy (NRT) and bupropion for smoking cessation, this was adopted by the Health Technology Board for Scotland who advised that it was valid for Scotland.

In March 2006, NICE issued its first Public Health Intervention Guidance (PHIG), Brief Interventions and Referral for Smoking Cessation in Primary Care and Other Settings (NHS QIS has not commented on this guidance).

There is further NICE PHIG guidance in progress; the final scope has been posted on the website with the guidance expected to be published in November 2007. Smoking Cessation. Guidance on the optimal provision of smoking cessation services including the provision of NRT, for primary care, pharmacies, local authorities and workplaces with particular reference to manual groups, pregnant smokers and hard to reach communities. This guidance includes all factors which might influence smoking cessation including some social factors and the nature of the intervention.

Varenicline is subject to a NICE Single Technology Assessment (STA) which is expected to be published in 2007.

Additional information: comparators

Bupropion SR, and nicotine replacement therapies (NRT).

Additional information: costs

Drug	Dose	Cost per treatment course (£)
Varenicline	Initial titration then 1mg twice daily for 12-24 weeks	164 - 328
Bupropion SR	Initial titration then 150mg twice daily for 7-9 weeks	61-80
Nicotine replacement therapy (NRT) patches	5-15mg patch applied daily for 12 weeks	109-120

Costs were taken from the eVadis database accessed on 3rd October 2006. Doses shown are for general comparison and do not imply therapeutic equivalence

Additional information: budget impact

The manufacturer estimates that the net budget impact of varenicline on the prescribing budget will be £455k in yr 1 and £2.6m in year 5, based on 5,700 patients and 34,400 patients respectively. This assumes:

- (i) Scots who stated in a 2005 survey of attitudes to smoking they would quit within a year actually do so. It seems likely that some people who say they will try to quit will not actually do so.
- (ii) Currently 16% of smokers trying to quit get either NRT or bupropion. The submission claims, with no explanation, that this will increase to 29% over the next five years.
- (iii) That 32% of patients treated will receive an additional 12 week course of treatment.

Other data were also assessed but remain commercially confidential.*

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 17 November 2006.

** Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: <http://www.scottishmedicines.org.uk/>*

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

The undernoted references were supplied with the submission.

Gonzales D, Rennard S, Nides M et al. Varenicline, an $\alpha 4\beta 2$ nicotine acetylcholine receptor partial agonist vs sustained-release bupropion and placebo for smoking cessation. A randomised controlled trial. JAMA 2006; 296: 47-55.

Jorenby DE, Hays JT, Rigotti NA et al. Efficacy of Varenicline, an $\alpha 4\beta 2$ nicotine acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation. A randomised controlled trial. JAMA 2006; 296: 56-63

Tonstad S, Tonnesen P, Hajek P et al. Effect of Maintenance Therapy with Varenicline on Smoking Cessation. A randomised controlled trial. JAMA 2006; 296: 64-71

Klesges RC, Johnson KC, Somes G. Varenicline for Smoking Cessation. Definite promise, but no panacea. JAMA 2006;296:94-95