

NEW DRUG EVALUATION

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VARENICLINE

Varenicline (Champix[®]▼) is a partial nicotinic receptor agonist licensed to aid smoking cessation. To date, there is no published evidence from randomised controlled trials comparing varenicline with the most commonly prescribed cessation aid, nicotine replacement therapy. Furthermore, safety has not been established in patients with medication controlled diabetes, significant cardiovascular disease or uncontrolled hypertension. Particular caution is necessary in patients with a previous history of psychiatric illness; depression and suicidal ideation or attempt, have been reported in patients treated with varenicline. In published trials, 44% of patients taking varenicline for 12 weeks abstained from smoking during weeks 9-12 compared with 30% on bupropion and 18% on placebo. However, all subjects received concomitant motivational support at a level that would not be expected in routine clinical practice. Current evidence does not suggest that a subsequent 12-week treatment course significantly improves long-term (52-week) cessation rates. Varenicline is an option for smoking cessation in patients in whom the benefits are considered to outweigh possible risks and the increased cost over some more established options.

PRACTICE POINTS - prescribing advice

- Smoking cessation, with or without medication, may exacerbate an underlying psychiatric condition, including depression. Care should be taken in such patients, who should be advised of this risk.
- Varenicline should be prescribed with caution in patients with a previous history of psychiatric illness.
- Depression, including suicidal ideation and attempt, have been reported in patients trying to stop smoking using varenicline; patients should be advised of the risks.
- Patients taking varenicline who develop suicidal thoughts should stop their treatment and contact their doctor immediately.
- Healthcare professionals should monitor patients taking varenicline for changes in behaviour and / or mood.
- Varenicline can influence the ability to drive and use machinery; patients should be advised not to drive until they know whether varenicline affects their capability.
- All suspected adverse reactions to varenicline should be reported to the MHRA using a Yellow Card.

What is it?

Varenicline (Champix[®]▼, Pfizer) is a partial agonist selective for nicotinic acetylcholine receptor subtypes and is licensed as an aid to smoking cessation.^[1] It is available in 0.5 mg and 1 mg tablets with the recommended dose being titration with 0.5 mg tablets for one week, followed by 1 mg twice daily for 11 weeks. Dosing should start one to two weeks before the planned cessation date and tablets can be taken with or without food.^[1]

How effective is it ?

Two multi-centre, randomised, double-blind, placebo-controlled trials involving 1,025 and 1,027 patients compared varenicline with bupropion and placebo.^[2, 3]

Eligible subjects received either 1 mg varenicline twice daily, 150 mg bupropion twice daily or placebo for 12 weeks (which included dose titration of active treatments for one week). Subjects with medication controlled diabetes mellitus, significant cardiovascular disease or uncontrolled hypertension were excluded.^[2, 3] The primary end point was continuous abstinence during weeks 9 and 12. In both studies varenicline was significantly more effective than both bupropion (44% vs. 29.5%, $p < 0.001$ ^[2] and 43.9% vs. 29.8%, $p < 0.001$ ^[3]) and placebo (44.0% vs. 17.7%, $p < 0.001$ ^[2] and 43.9% vs. 17.6%, $p < 0.001$ ^[3]). Longer-term abstinence was also evaluated by assessing cessation rates from weeks 9 to 52.

Varenicline was significantly more effective than bupropion in one trial (23% vs. 14.6%, $p = 0.004$ ^[3]) and placebo in both trials (21.9% vs. 8.4%, $p < 0.001$ ^[2] and 23% vs. 10.3%, $p < 0.001$ ^[3]). These results may be considered to more closely reflect likely differences between interventions in the longer term, as benefits from smoking cessation are realised only over an extended period.

An extension trial compared varenicline with placebo for a further 12-week course from weeks 13 to 24.^[4] All subjects ($n = 1,927$) initially received varenicline 1 mg twice daily for 12 weeks. Subjects who did not smoke during the last seven days of those 12 weeks were subsequently randomised to receive a further 12-week course of varenicline ($n = 603$) or placebo ($n = 607$). The confirmed continuous abstinence rates at 24 weeks were 70.5% and 49.6% for varenicline and placebo respectively ($p < 0.001$). The 52-week abstinence rates were 43.6% and 36.9% respectively ($p = 0.02$).^[4] It is noteworthy that over a third ($n = 691$) of the original participants were not eligible for randomisation after the 12-week open-label phase.^[4] Consequently a large proportion of participants for whom varenicline may have been ineffective were eliminated from the final analysis. This potentially biases the results in favour of treatment with varenicline. If the final analysis includes these ineligible patients as failures ($n = 1,294$) then the 11- to 52-week abstinence rates for those taking the drug for 24 weeks are actually lower than for those taking the drug for 12 weeks in the companion studies.^[5]

Furthermore all patients had access to 18^[2,3] or 20^[4] ≤ 10 minute counselling sessions, including one per week for the 12-week treatment phase. This level of support may not be available in practice, which could lead to lower response rates than those observed in the clinical trials.

A recent systematic review of varenicline conducted by the Cochrane Collaboration includes the data discussed here.^[6] It highlights the need for further independent, comparator trials to establish varenicline's relative efficacy and safety.^[6]

A non-randomised comparison of short-term smoking cessation rates with varenicline and nicotine replacement therapy (NRT) in 412 patients attending an NHS tobacco dependence clinic in the periods before and after the introduction of varenicline, suggested that varenicline is more effective than NRT. At four weeks after quit day 72.1% and 61.3% patients respectively were abstinent (odds ratio 1.63 [95% CI 1.08 to 2.47]).^[7] A sub-analysis of combination and single-product NRT versus varenicline showed that varenicline was significantly more effective than single-product NRT, but not combination NRT, although the statistical power was inadequate to test the latter (cessation rates 72.1%, 57.9% and 66.3%, respectively; odds ratio 1.88 [95% CI 1.18-3.02] for varenicline versus single-product NRT).^[7] Further evidence, ideally from randomised controlled trials, is required to determine varenicline's place in therapy.

How safe is it?

The most commonly reported adverse effect was nausea with a markedly higher rate in subjects taking varenicline than bupropion and placebo (28-29%, 7-13%, 8-10% respectively).^[2, 3] Most reports were however of mild to moderate severity. Abnormal dreams were also more common in subjects taking varenicline (10-13%, 6%, 4-6% respectively).^[2, 3] The incidences of headache and insomnia were also high although levels were only slightly higher for those on varenicline than placebo. Despite these side effects, which mainly occur during the first four weeks of treatment,^[8] discontinuation rates with varenicline were comparable with bupropion and placebo.^[2-4] Patients who had required treatment for depression in last 12 months were excluded from the clinical trials, as were patients with a history of psychiatric illness,^[2-4] and the manufacturer cautions against the use of varenicline in such patients.^[1]

Post marketing safety review

Since its launch in the UK in December 2006, around 200,000 people have used varenicline.^[9] Up to the end of December 2007, the Medicines and Healthcare products Regulatory Authority (MHRA) had received 1,603 reports of suspected adverse drug reactions in relation to the use of varenicline.^[9] Most of the reports are to well recognised reactions, such as: abnormal dreams, 95 reports; fatigue and malaise, 141; headache, 166; insomnia, 82; nausea, 427; vomiting, 140.^[9] As varenicline is reported to cause dizziness and somnolence (93 and 49 reports respectively), healthcare professionals are reminded of the possible effects of varenicline on driving and patients should be advised not to drive until they know whether varenicline is likely to affect their driving ability.^[1,10]

Recent concerns regarding reports of suicidal thoughts and behaviour in association with varenicline have prompted a Europe-wide review of safety data.^[11] The MHRA received 62 reports of depressed mood, generally in patients with a previous psychiatric history, and 54 reports of suicidal ideation up to the end of December 2007.^[9,10] The European Medicines Agency has recommended that the Summary of Product Characteristics for varenicline be updated to contain warnings that depression, including suicidal thoughts and behaviour, has been reported in patients who are undergoing a smoking cessation attempt and that these symptoms have been reported in patients treated with varenicline.^[12] Further prescribing guidance is detailed in the **Practice Points** section.^[11-13] A preliminary assessment of cases of suicidal ideation by the US Food and Drug Administration revealed that in many cases new onset of depressed mood, suicidal ideation and changes in emotion and behaviour occurred within days to weeks of initiating varenicline.^[13] However, the role of varenicline in such cases is unclear as depressed mood may be a symptom of nicotine withdrawal, and smoking cessation, with or without medication, may exacerbate an underlying psychiatric condition.^[10,12]

What other options are there?

Current licensed alternative smoking cessation aids are NRT and bupropion. It is recommended that smoking should stop completely before starting a smoking cessation regime with NRT. Counselling should also be available for behavioural support.^[14] The National Institute for Health and Clinical Excellence (NICE) has previously published guidance on the use of NRT and bupropion in smoking cessation, recommending either for smokers who have expressed a desire to quit smoking.^[14] Recently published NICE guidance recommends that varenicline be an option, within its licensed indications, for smokers who have expressed a desire to quit smoking, and should be prescribed only as part of a programme of behavioural support.^[16]

When should it be used?

There is very little published evidence to suggest that varenicline has a clear clinical advantage over the most widely prescribed smoking cessation aid, NRT. There is limited data suggesting a higher smoking cessation rate for patients taking varenicline when compared to bupropion. When choosing a smoking cessation aid, prescribers should take into account the adverse event profile and relative cost of each agent. With these factors in mind, varenicline may be an alternative to bupropion where NRT is contraindicated or not tolerated. Varenicline is not recommended for use in children or adolescents <18 years of age.^[1] The safety and efficacy of varenicline in patients with medication controlled diabetes, uncontrolled hypertension or significant cardiovascular disease has not been established and it should be prescribed with caution in patients with a previous history of psychiatric illness.

When should adverse drug reactions be reported to the MHRA?

All suspected adverse reactions to black triangle drugs, such as varenicline, should be reported to the MHRA via the Yellow Card Scheme www.yellowcard.gov.uk. This includes depression, suicidal ideation and psychiatric reactions thought to be related to varenicline.

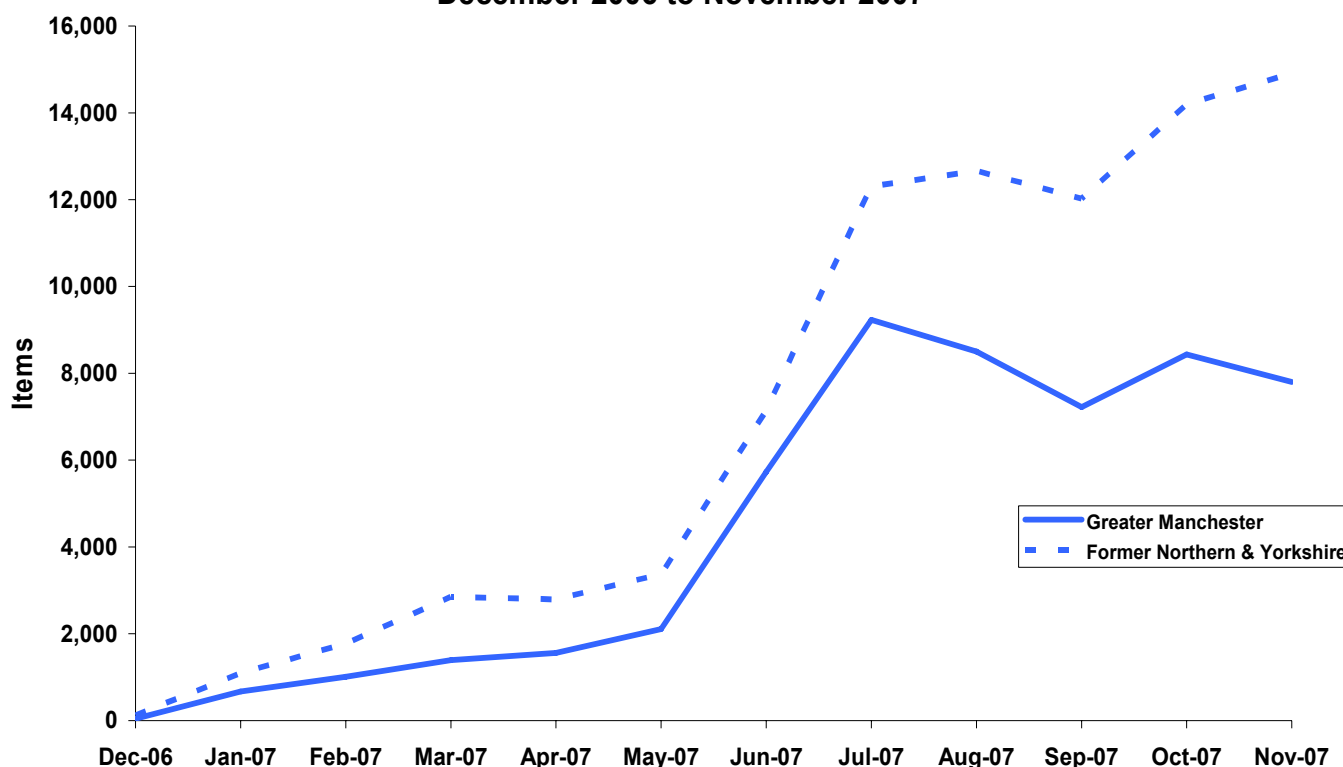
All suspected serious reactions to any drug, herbal or OTC medicines should also be reported. Further guidance on the reporting of adverse reactions is available from the Yellow Card Centre Northern and Yorkshire website www.nyrdtc.nhs.uk.



How much varenicline has been prescribed?

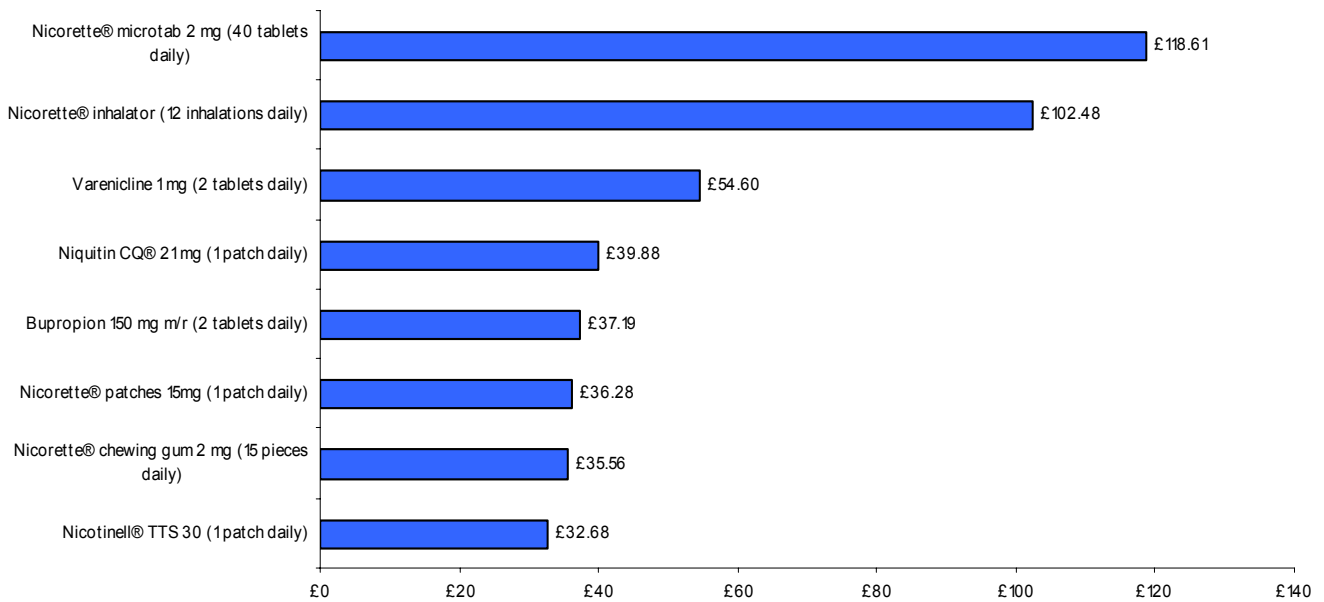
Since it was launched in December 2006, uptake of varenicline in primary care has been extremely rapid. From December 2006 to November 2007, 85,248 items (at a cost of £2,903,123) and 53,702 items (at a cost of £1,988,771) were dispensed in the former Northern & Yorkshire region and the PCTs of the former Greater Manchester SHA, respectively. The prescribing frequency trends are shown in the figure below; the trend for England is similar. A marked increase in prescribing occurred in the two months preceding the ban on smoking in public places in England in July 2007.

North of England: Prescribing frequency of varenicline
December 2006 to November 2007



How much does it cost?

Cost of 28 days treatment (Drug Tariff/ eMIMS January 2008)



The NRT preparations selected were the most commonly prescribed NRT preparations in the North of England in the 2005/06 financial year. Doses shown are for general comparison only and do not imply therapeutic equivalence.

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KEY RCT - randomised controlled trial, G – guideline, R - Review

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