

# Varenicline (Champix) for smoking cessation

(VA-ren-i-kleen)

## Summary

- Varenicline is a non-nicotine drug for smoking cessation. It has a different mechanism of action to that of other smoking-cessation drugs.
- In clinical trials of generally healthy, motivated smokers, more people using varenicline (23%) had quit smoking at 1 year compared with those using bupropion or placebo (15% and 10%, respectively).
- Varenicline should only be prescribed in conjunction with a comprehensive smoking-cessation support and counselling program.
- Nausea was the most common adverse effect of varenicline in clinical trials (around 30%) leading to treatment withdrawal in around 3% of people. Other common adverse effects included insomnia, abnormal dreams, headache and constipation.
- The safety and efficacy of varenicline in smokers with serious medical or psychiatric illness has not been established.
- Monitor all patients for behaviour and/or mood changes, because of post-marketing reports of psychiatric symptoms associated with varenicline use.
- The effectiveness of varenicline on long-term abstinence rates beyond 12 months has not been studied.
- Varenicline is subsidised on the PBS for one 12-week course of treatment per patient per year.
- The safety and efficacy of varenicline in combination with bupropion and other pharmacological therapies for smoking cessation has not been established.

## PBS listing

Only one full course of Pharmaceutical Benefits Scheme (PBS)-subsidised varenicline will be authorised per person per year. The period between starting a course of varenicline and a course of bupropion for smoking cessation must be at least 6 months. A course of treatment with varenicline is 12 weeks and requires 2 prescriptions; the first for an initial 4 weeks of treatment (including dose titration) and the second for a further 2 months of treatment.

Clinical review is recommended within 2–3 weeks of the first prescription request.

## Authority required

For smoking cessation in people who wish to stop smoking and have entered, or who are entering at the time of the initial authority prescription request, a comprehensive support and counselling program for smoking cessation. Details of the program must be specified in the original authority request.

## Reason for PBS listing

The Pharmaceutical Benefits Advisory Committee accepted that varenicline users achieved higher quit and continuous abstinence rates than bupropion users and recommended varenicline for listing on the basis of an acceptable cost-effectiveness compared with bupropion.<sup>1</sup>

To limit wastage when people discontinue early in treatment, the Committee recommended that treatment begin with a 4-week course of varenicline. For people tolerating varenicline who remain motivated to quit, this can be followed by a further 8 weeks of treatment (12 weeks in total).<sup>1</sup>

## Place in therapy

Varenicline is a nicotinic acetylcholine-receptor partial agonist\* used for smoking cessation. It is thought to work by reducing craving and withdrawal symptoms, and by reducing reinforcement of the smoking habit due to its satisfying or enjoyable effects.<sup>2</sup>

In directly comparative trials, smokers randomised to varenicline achieved higher continuous smoking abstinence<sup>†</sup> rates at 12, 24 and 52 weeks after starting a 12-week course of therapy than those randomised to bupropion or placebo<sup>3,4</sup>, although the proportion of smokers who remained abstinent decreased over time (see Figure 1).

Importantly, these trials involved generally healthy, motivated quitters who received regular smoking cessation support and advice. The effectiveness of varenicline in the general smoking population may be lower.

Without a head-to-head comparison trial it is unclear how much varenicline's effectiveness differs from that of nicotine replacement therapy.

Varenicline's effect on relapse and abstinence rates beyond 12 months has not been studied.

\* In the absence of nicotine, varenicline activates nicotinic acetylcholine receptors (agonist activity). In the presence of nicotine, varenicline blocks nicotine's ability to bind with these receptors (antagonist activity).<sup>2</sup>

† Continuous smoking abstinence was assessed as a self-report of no smoking (not even a puff) or use of other nicotine-containing products since the previous visit or contact, confirmed by measuring expired carbon monoxide levels.<sup>3,4</sup>

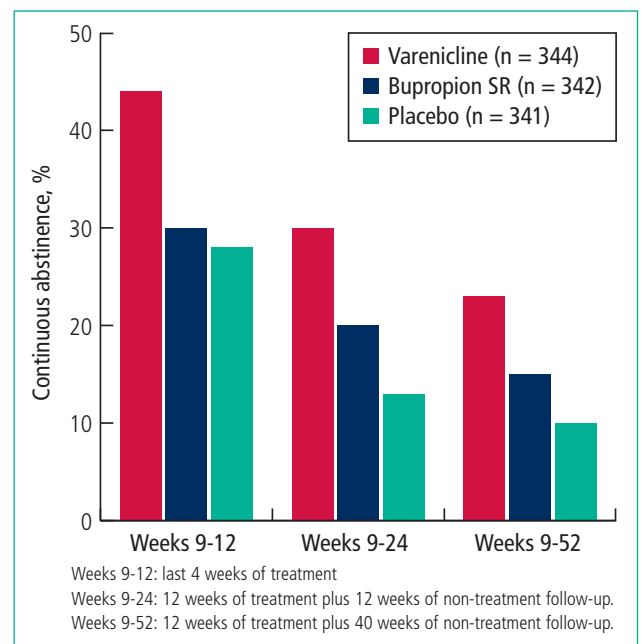
## The effect of pharmacotherapy on quit rates declined over time

In clinical trials, continuous abstinence rates during the last 4 weeks of a 12-week treatment course were considerably higher for varenicline-treated smokers than for those treated with bupropion (44% versus 30% for bupropion,  $p < 0.001$ ) or placebo (44% versus 18% for placebo,  $p < 0.001$ ).<sup>3,4</sup> Longer-term continuous abstinence rates (6 months and 1 year after starting therapy) remained higher for varenicline-treated smokers.<sup>3,4</sup> Abstinence rates declined in all study groups after the end of treatment; however, the relative differences between treatment groups were maintained (see Figure 1). In one trial, by the end of a 52-week period (12 weeks of treatment and 40 weeks of follow-up) 23% of the varenicline group remained continuously abstinent, compared with 15% of the bupropion group (odds ratio [OR] 1.77,  $p = 0.004$ ) and 10% of the placebo group (OR 2.66,  $p < 0.001$ ).<sup>3</sup> Similar results were achieved in a second varenicline trial that was identical in design.<sup>4</sup>

Varenicline's effect on relapse rates beyond 12 months is unknown.

In another study, an additional 12 weeks of varenicline for successful quitters (24 weeks of varenicline in total) improved continuous abstinence rates during weeks 13 to 52 compared with placebo (44% versus 37% with placebo,  $p = 0.02$ )<sup>5</sup>; however, treatment for longer than 12 weeks is not covered under the current PBS listing.

Figure 1. Continuous smoking abstinence rates<sup>3</sup>



## The effectiveness of varenicline in real life is uncertain

Real-life adherence and quit rates with varenicline may be lower than in trials. Importantly, all clinical trial participants received a level of support unlikely to be available in general practice. This involved smoking-cessation counselling and follow-up support including a booklet at the start of treatment, up to 10 minutes smoking-cessation counselling at each clinic visit (weekly clinic visits during the 12-week treatment phase) and a telephone call 3 days after the expected quit date.<sup>3,4</sup>

Several other factors limit the generalisability of varenicline trial results to a broader population of smokers. These include broad medical and psychiatric exclusion criteria applied in the trials and the moderate level of nicotine dependence of trial participants (mean Fagerstrom score < 6, on a scale of 0–10). In addition, it is unknown if previous bupropion use or concurrent use of nicotine replacement therapy<sup>‡</sup> changes the effectiveness of varenicline. Key trials excluded people who had used bupropion at any time in the past, or any form of nicotine replacement therapy in the month before enrolling in the trials.<sup>3,4</sup>

There are no data on the effectiveness of varenicline when a previous quit attempt with varenicline was unsuccessful.

## Counselling and support are essential

All smokers, whether motivated to quit or not, should be offered at least minimal smoking-cessation advice (brief advice) by health professionals.<sup>7,8</sup> Consider smoking-cessation drug therapies for smokers who want to quit. Combine drug therapies with appropriate behavioural and psychosocial support to maximise the person's chances of successfully quitting.<sup>7,8</sup> There is evidence that more intensive smoking cessation interventions are more effective than less intensive ones.<sup>9,10</sup> Refer to *NPS News 45* on chronic obstructive pulmonary disease for more information about interventions for smoking cessation.

<sup>‡</sup> A cross-sectional survey of general practice activity in Australia during 2002 and 2003 (n = 2207) found that, in their last quit attempt, an estimated 13% of adult smokers had tried bupropion and an estimated 35% had tried nicotine replacement therapy.<sup>6</sup>

## Smoking remains a major public health concern in Australia

Despite declining smoking rates over recent years, around 1 in 5 Australians over the age of 18 years smokes on a daily basis.<sup>11,12</sup> An estimated 40% of smokers in Australia attempt to quit each year but fewer than 10% manage to successfully stop smoking for 1 month or longer.<sup>13</sup> Most people make several serious attempts to quit before successfully stopping.<sup>7</sup>

## Safety issues

Treatment-related adverse effects reported more commonly with varenicline than with placebo include nausea (29% versus 9%), insomnia (14% versus 11%), abnormal dreams (12% versus 5%), headache (10% versus 8%) and constipation (6% versus 2%).<sup>2</sup>

Varenicline is a new drug in a new class of drugs, therefore some extra uncertainty exists about its safety profile. While no additional safety concerns were identified in clinical trials that included around 4000 people given varenicline, the possibility of unexpected adverse drug effects cannot be ruled out until varenicline is used in larger numbers of smokers. Possible psychiatric effects have been reported with varenicline since its launch in the US and Europe (see below).

Varenicline has no known clinically meaningful interactions with other drugs.<sup>2</sup> However, smoking and smoking cessation with or without drug therapy, can affect the pharmacokinetic and pharmacodynamic properties of some drugs, and dose adjustments may be required.<sup>2,14</sup>

## Varenicline causes nausea

In clinical trials around 30% of smokers who received varenicline experienced nausea.<sup>2–5</sup> Nausea was also the most common reason for treatment withdrawal in smokers using varenicline (3% versus 0.6% receiving placebo).<sup>2</sup> Tell people that they may experience nausea and that taking varenicline with food and a full glass of water may help.<sup>15</sup> One trial found nausea to be dose related.<sup>16</sup> Although the efficacy of lower doses of varenicline is unknown, slower dose titration (see Dosing issues) may be helpful for people unable to tolerate the target dose of varenicline (1 mg twice daily) because of nausea.

## Monitor patients for possible psychiatric adverse effects

Post-marketing reports of new onset of depressed mood, aggressive and erratic behaviour, suicidal thoughts and suicide within days to weeks of starting varenicline include patients with and without pre-existing psychiatric illness.<sup>2,17,18</sup> Isolated exacerbations of underlying psychiatric illnesses (e.g. schizophrenia, bipolar disorder) have been reported with varenicline use.<sup>19,20</sup> Until more data are available, consider the benefits and risks of prescribing varenicline for people with a current or past history of psychiatric illness. Ask all patients about any changes in mood or behaviour after starting varenicline, during the 2–3-week follow-up visit and after treatment is completed.

Guidelines recommend careful monitoring of all people with underlying psychiatric illnesses who are quitting smoking. This is because of the possible effects of smoking cessation (with or without drug therapy) on their illness and medication.<sup>7,21</sup>

## Other safety considerations

Be aware of the following:

- The safety and efficacy of varenicline have not been established in people with unstable intercurrent medical illnesses. Prescribe varenicline with caution in these people.
- Treatment withdrawal (after 12 weeks) may cause increased irritability, urge to smoke, depression, and sleep disturbances in up to 3% of people.<sup>2</sup>
- The safety and efficacy of varenicline in combination with bupropion have not been established and these drugs should not be used together.<sup>2</sup>
- Combining varenicline with nicotine replacement therapy causes an increase in nausea, headache, dyspepsia, fatigue and dizziness and a small decrease in average systolic blood pressure (2.6 mmHg)<sup>2</sup>, and is not recommended.
- The safety of varenicline has not been established in pregnant or breastfeeding women or in people < 18 years.<sup>2</sup>

Report suspected adverse reactions to the Adverse Drug Reactions Advisory Committee (ADRAC) online ([www.tgasime.health.gov.au](http://www.tgasime.health.gov.au)) or by using the 'Blue Card' distributed with Australian Prescriber. For information about reporting adverse reactions, see the Therapeutic Goods Administration website ([www.tga.gov.au](http://www.tga.gov.au)).

## Dosing issues

People should set a date to stop smoking. Start varenicline 1–2 weeks before their quit date.<sup>2</sup> Titrate the dose as follows:

- days 1–3: 0.5 mg daily;
- days 4–7: increase to 0.5 mg twice daily; and
- continue with 1 mg twice daily from day 8 to the end of a 12-week treatment course.

The initiation pack contains 11 × 0.5 mg, 14 × 1 mg and 28 × 1 mg varenicline tablets. The second prescription contains 2 boxes of 56 × 1 mg tablets. A phone call from a GP or practice nurse around the planned quit date may be helpful.<sup>10</sup> Make an appointment for follow-up 2–3 weeks after the original prescription to provide the second prescription and to monitor progress and provide additional support.

For people with creatinine clearance < 30 mL/min the recommended daily dosage is 1 mg daily (0.5 mg daily for 3 days then increasing to 1 mg daily).<sup>2</sup> Avoid varenicline in end-stage renal failure in favour of other approaches to smoking cessation. Dose adjustment is not routinely required in the elderly or in people with hepatic impairment.<sup>2</sup>

## Information for patients

Advise patients of the following:

- Varenicline frequently causes nausea, which may settle over time. Taking varenicline with food and a full glass of water may help reduce nausea.<sup>15</sup> Ask people to tell their doctor if nausea is severe or prevents them from taking their medication.
- Set a date to stop smoking and start varenicline 1–2 weeks before (to reduce craving and withdrawal symptoms).<sup>2</sup>

- Do not use nicotine-containing therapies while using varenicline; using nicotine replacement at the same time may cause nausea, headache, dyspepsia, fatigue and dizziness.<sup>2</sup>
- Smoking cessation advice, information and support can increase their chances of quitting successfully. Advise people to follow the smoking-cessation program recommended by their doctor, pharmacist or health professional. Advise them about additional smoking-cessation services available in their area and how to access them if necessary.
- To contact a doctor if they are concerned about any changes in their mood or normal behaviour patterns while taking varenicline.<sup>15,17,18</sup>
- Varenicline can cause dizziness and sleepiness in some people. Advise people to be cautious when driving or operating machinery until they know how varenicline affects them.<sup>2</sup>
- At the end of treatment with varenicline some people (3% in clinical trials) experience increased irritability, urge to smoke, depression and/or insomnia.
- Varenicline does not cause weight gain directly, but about 75% of people who stop smoking with any method experience a small amount of weight gain (2–

4 kg).<sup>8</sup> In clinical trials people taking varenicline experienced a weight gain of about 3 kg, which was similar to that seen in people taking placebo.<sup>3,4</sup>

- Varenicline is a new medicine and as such may have unwanted effects that have not yet been identified. Tell people to report any possible side effects to their doctor, pharmacist or health professional.

Suggest or provide the Champix consumer medicine information (CMI) leaflet.

### Medicine Update

An NPS *Medicine Update* leaflet on varenicline is available for consumers. *Medicine Update* helps consumers to ask the right questions about new medicines and helps them compare the potential benefits and harms of a new medicine with other medicines.

For more information about smoking and smoking-cessation programs call the Quitline 131848 or visit the National Tobacco Campaign website ([www.quitnow.info.au](http://www.quitnow.info.au)).

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The information contained in this material is derived from a critical analysis of a wide range of authoritative evidence. Any treatment decisions based on this information should be made in the context of the clinical circumstances of each patient.