

Varenicline (Champix)

for smoking cessation

(VA-ren-i-kleen)

Consider medical and psychiatric history before prescribing

KEY POINTS

Varenicline is a non-nicotine drug for smoking cessation

It has a different mechanism of action from that of other smoking cessation drugs.

Quit rates at 1 year were greater with varenicline (23%) than with bupropion (15%) or placebo (10%)

The effect of varenicline on abstinence rates beyond 12 months has not been studied.

Prescribe varenicline together with a support and counselling program

All participants in key trials with varenicline received comprehensive counselling and support.

Consider other treatment options for people with serious psychiatric or medical illnesses (e.g. epilepsy, chronic obstructive pulmonary disease, cardiovascular disease)

The safety and efficacy of varenicline for people with these conditions is uncertain.

Thirty per cent of people experienced nausea in clinical trials

Insomnia, abnormal dreams, headache and constipation were also common adverse effects.

Serious psychiatric adverse events have been reported in people with and without a history of psychiatric illness

Advise all patients to stop varenicline and to see a doctor as soon as possible if they experience any unusual or serious change in mood, thinking or behaviour.

Varenicline may cause a small increase in risk of serious cardiovascular events.

Advise all patients that the risk appears to be small, but to seek medical attention as soon as possible if they experience new or worsening symptoms of cardiovascular disease (e.g. chest pain, shortness of breath).



EVIDENCE SNAPSHOT

WHAT IS KNOWN ABOUT THIS DRUG

A meta-analysis found that the abstinence rate at ≥ 24 weeks for a 12-week course of varenicline plus counselling was more than twice that of counselling alone (risk ratio 2.3 [95% confidence interval (CI) 2.0 to 2.7]).¹ Pooled data from 3 trials found that more people were abstinent at 12 months with varenicline than with bupropion (risk ratio 1.5 [95% CI 1.2 to 1.8]).¹

AREAS OF UNCERTAINTY

There are limited data comparing the effectiveness of varenicline with nicotine replacement therapy. The effect of previous bupropion use or concurrent use of nicotine replacement therapy on varenicline is unknown. Psychiatric symptoms, including suicidal behaviour, have been reported with varenicline, but a causal link has not been established. Serious cardiovascular events have been reported with varenicline, but the size of any increased risk is uncertain.

WHAT DOES NPS SAY?

Varenicline is an option for smokers who are nicotine dependent and are motivated to quit. Varenicline must be prescribed in conjunction with a comprehensive smoking cessation support program. Nicotine replacement therapy is the preferred smoking cessation drug for people with psychiatric illness and for people with stable cardiovascular disease.

PBS listing

Authority required

Short-term therapy for smoking cessation, as an aid for motivated people who wish to quit smoking.

- ▶ First 4 weeks: smoking cessation for people who wish to stop smoking and have entered a comprehensive support and counselling program for smoking cessation, or enter such a program at the time of the request. Details of the program must be specified in this request.
- ▶ Further 8 weeks: continuation of smoking cessation for people who have completed the first 4 weeks of therapy with varenicline.
- ▶ Extra 12 weeks: extension of smoking cessation therapy for people who have stopped smoking* and have completed 12 weeks of therapy with varenicline.

Under the subsidy, people starting varenicline:

- ▶ must not be taking other PBS-subsidised treatments for smoking cessation
- ▶ must not have started varenicline within the past 12 months or bupropion within the past 6 months

- ▶ must be enrolled in a comprehensive support and counselling program for smoking cessation and remain enrolled for the full course of varenicline
- ▶ should be clinically reviewed within 2–3 weeks of their first prescription.

May be prescribed by nurse practitioners

Authorised nurse practitioners may prescribe this medicine on the PBS. See the PBS website for more information on nurse practitioner PBS prescribing.[†]

What is it?

Varenicline is a nicotinic acetylcholine-receptor partial agonist[‡] used for smoking cessation.³

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.

Who is it for?

Consider varenicline for people who are motivated to quit smoking

Although data for varenicline show that it can double the chances of successful smoking cessation for up

*Not defined under the PBS listing. In a relevant clinical trial, 'stopped smoking' was defined as a self-report of no smoking or use of nicotine-containing products within the past 7 days — as well as having an end-expired CO ≤ 10 ppm.²

[†] www.pbs.gov.au/info/healthpro/explanatory-notes/section1/nurse-practitioner

[‡] In the absence of nicotine, varenicline partially activates nicotinic acetylcholine receptors (agonist activity).³ In the presence of nicotine, varenicline blocks nicotine's ability to bind with these receptors (antagonist activity).

to 12 months compared with no pharmacotherapy, there are important differences between study participants and smokers in the community.

Clinical trials of varenicline enrolled generally healthy, motivated quitters who received regular smoking cessation support and advice.⁴⁻⁶ Participants had moderate levels of nicotine dependence (mean Fagerström score < 6, on a scale of 0–10) and lacked coexisting psychiatric and medical conditions. The general smoking population is likely to include individuals with comorbidities and higher levels of nicotine dependence, either of which may adversely impact on adherence and quit rates with varenicline.

Avoid varenicline in people with a serious psychiatric or medical illness

Serious psychiatric events and serious cardiovascular events, including myocardial infarction and cerebrovascular accident, have been reported in people treated with varenicline (see Safety issues).³ Smokers with serious psychiatric illness (e.g. schizophrenia), or serious medical conditions (e.g. epilepsy, cardiovascular disease, or chronic obstructive pulmonary disease [COPD]), or a recent history of drug or alcohol abuse were excluded from key trials.^{3,7}

In a placebo-controlled trial involving 504 people with mild-to-moderate COPD, 12 weeks of varenicline was effective in improving abstinence rates at 52 weeks without causing a significant increase in serious adverse events.⁸ Although data were collected on lung function parameters and respiratory symptoms, these were not reported according to treatment assignment, so it is not clear if varenicline improves or worsens COPD in the short term.⁹ There are no data for use of varenicline in people with severe COPD.

The US Food and Drug Administration (FDA) reviewed data from a placebo-controlled trial involving around 700 smokers with stable cardiovascular disease. While 12 weeks of varenicline was effective in improving the 52-week abstinence rate, the drug was associated with an increase in some cardiovascular events compared with placebo, although this was not statistically significant (see Safety Issues). The FDA has advised that the known benefits of varenicline

should be weighed against the potential risks of its use in smokers with cardiovascular disease.^{10,11} There are no data for use of varenicline in people with unstable cardiovascular disease.

Effectiveness in real life is probably lower than in clinical trials

About 50% of Australians prescribed varenicline during the first 12 months of PBS listing stopped treatment within 4 weeks (defined as not filling their second prescription), while 11.4% of people who took varenicline in clinical trials discontinued over the course of the trial.^{3,12} The number of Australian smokers who quit successfully despite discontinuing varenicline is not known.

Where does it fit?

Choose smoking cessation therapy according to personal circumstances and preference

Smoking cessation pharmacotherapy, including varenicline, bupropion and nicotine replacement therapy (NRT), should be considered for smokers who are nicotine dependent and wish to quit.¹³ While trials have found differences in quit rates between drug options, personal circumstances and preference are probably more important considerations when selecting an appropriate smoking cessation aid.⁷ Refer to *NPS News 68: Helping smokers quit* for details of the relative advantages and disadvantages of first-line smoking cessation drugs.

Counselling and support are essential

All smokers, whether motivated to quit or not, should be offered at least brief smoking cessation advice from a health professional.^{13,14} Behavioural and psychosocial support of people taking a drug for smoking cessation maximises their chance of successfully quitting. There is no evidence that varenicline is as effective for smoking cessation without counselling and support.

The benefits and risks of combined therapy are unclear

It is not known if previous use of bupropion or varenicline, or concurrent use of nicotine replacement therapy, changes the effectiveness of varenicline. Combining varenicline with nicotine

replacement therapy is not recommended. It causes an increase in nausea, headache, dyspepsia, fatigue and dizziness, and a small decrease in average systolic blood pressure (2.6 mmHg).³ The safety and efficacy of varenicline in combination with bupropion have not been established. Key efficacy 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.^{4,5} One 24-week trial of varenicline allowed use of bupropion or nicotine replacement therapy up to one month before enrolment.²

How does it compare?

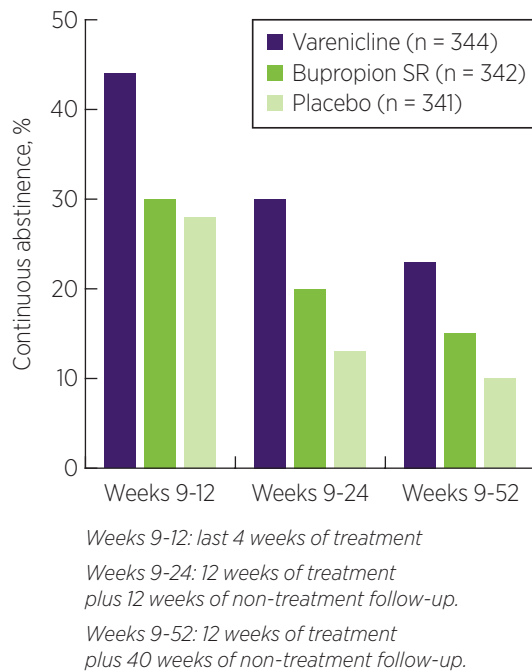
A meta-analysis of clinical trials found that people taking varenicline achieve higher continuous smoking abstinence rates than those taking placebo at 24 weeks or more (risk ratio 2.3, 95% CI 2.0 to 2.7).¹

Varenicline is more effective than bupropion

In randomised trials with a 12-week treatment period, abstinence rates* were higher with varenicline than with sustained-release bupropion or placebo at 12, 24 and 52 weeks (Figure 1).^{4,5}

* Continuous smoking abstinence was assessed as self-report of no smoking since the previous visit or contact, confirmed by measuring expired CO levels.

Figure 1. Continuous smoking abstinence rates⁴



Limited comparison with nicotine replacement therapy

In an unblinded comparison with nicotine replacement therapy, more people were abstinent during the last weeks of a 12-week course of varenicline than they were with a 10-week course of nicotine transdermal patches (56% vs 43%; $p < 0.001$).⁶ However, the difference in abstinence rates was smaller at 52 weeks (26% vs 20%; OR 1.4, 95% CI 0.99 to 1.99).

Abstinence rates decline over time

In clinical trials, continuous abstinence rates remained higher for varenicline-treated smokers 6 months and 1 year after starting therapy, but declined in all study groups during non-treatment follow-up (Figure 1). In one trial, at 1 year, 23% of the varenicline group remained abstinent, compared with 15% of the bupropion group (OR 1.77, $p = 0.004$) and 10% of the placebo group (OR 2.66, $p < 0.001$).⁴

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

Extension of therapy provides modest benefit

An additional 12 weeks of varenicline for successful quitters (24 weeks of varenicline in total) produced a small improvement in continuous abstinence rates during weeks 13–52 compared with placebo (44% vs 37%; $p = 0.02$).²

Safety issues

Common adverse effects reported more frequently with varenicline than placebo include nausea, insomnia, abnormal dreams, headache and constipation.³

Serious postmarketing adverse events include Stevens–Johnson syndrome, erythema multiforme, myocardial infarction, cerebrovascular accident (including ischaemic and haemorrhagic events), hallucinations, unusual or serious changes in behaviour or thinking, psychosis, suicidal ideation and suicide.³

Report suspected adverse reactions to the Therapeutic Goods Administration (TGA) online (www.ebs.tga.gov.au) or by using the 'Blue Card' distributed three times a year with *Australian Prescriber*. For information about reporting adverse reactions, see the TGA website (www.tga.gov.au).

Varenicline causes nausea

Nausea occurred in about 30% of smokers who received varenicline in clinical trials²⁻⁵ and was the most common reason for treatment withdrawal (3% vs 0.6% receiving placebo).³ Slower dose titration may be helpful for people unable to tolerate the varenicline maintenance dose because of nausea (see Dosing issues).

Avoid varenicline in people with a serious psychiatric or medical illness^{3,7}

Exacerbations of psychiatric illness (e.g. schizophrenia), seizures, tremors and muscle spasms have been reported in people taking varenicline.^{3,15-18} The safety and efficacy of varenicline has not been established for people with serious psychiatric or medical illness (including COPD, epilepsy or cardiovascular disease), who were excluded from clinical trials.

The FDA has advised that varenicline may be associated with a 'small increased risk of certain cardiovascular adverse events in patients who have cardiovascular disease', based on a trial involving around 700 people with stable cardiovascular disease*.¹¹ In this trial, serious cardiovascular events were reported in more people treated with varenicline than people treated with placebo although the differences were not statistically significant: non-fatal MI (2% vs 0.9%), need for coronary revascularisation (2.3% vs 0.9%), new diagnosis of peripheral vascular disease or admission for a procedure to treat PVD (1.4% vs 0.9%).¹⁹ The FDA has asked the drug sponsor to conduct a meta-analysis of trials.¹¹ See Modest evidence to support use of varenicline in cardiovascular disease.

* The study excluded smokers who had a recent cardiovascular event, and was not powered to detect small differences in cardiovascular event rates¹⁹

† Adjusted for confounders including sex, age, psychiatric history

Advise patients about possible serious psychiatric adverse effects

Serious psychiatric effects have been reported in people taking varenicline, including:^{3,15,20-23}

- ▶ depressed mood
- ▶ agitation
- ▶ hallucinations
- ▶ unusual or serious changes in behaviour or thinking
- ▶ anxiety
- ▶ psychosis
- ▶ mood swings
- ▶ aggressive and hostile behaviour
- ▶ suicidal thoughts and suicide attempts.

Psychiatric symptoms have occurred in people who stopped smoking and in people who continued to smoke.^{3,24} Reports include exacerbations of illness, as well as new-onset symptoms.^{3,25}

The FDA reviewed reports of suicidal thinking and suicidal behaviour in people who started varenicline over an 18-month period.²¹ Of 128 suicidal events in which timing was reported, the median onset was 2 weeks, with 86% of events occurring during varenicline therapy. About half the reported suicidal events occurred in people without a history of psychiatric illness.

A UK cohort study found no clear evidence of an increased risk of self-harm with varenicline (hazard ratio 1.12†, 95% CI 0.67 to 1.88 compared with nicotine replacement therapies). However, because of the wide confidence interval an increased risk of self-harm with varenicline could not be ruled out. Rates of self-harm, suicidal thoughts and depression among 80,660 people prescribed a smoking cessation agent were: varenicline (18 cases in 10,973 people) or bupropion (nine cases in 6422 people) compared with nicotine replacement therapies (141 cases in 63,265 people).²⁶

Advise everyone starting varenicline about the possibility of psychiatric events (see Information for patients).^{3,27}

Check for any unusual or serious changes in mood or behaviour at the 2- to 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.

Advise patients about possible small increased risk of cardiovascular events

A meta-analysis of 14 placebo-controlled trials in a total of 8216 people reported an association between varenicline and an increased risk of serious cardiovascular events (odds ratio [OR] 1.72, 95% confidence interval [CI] 1.09 to 2.71). Most people included in the research had no recent history of cardiovascular disease, but about 700 had known stable cardiovascular disease.²⁸

Consider other treatment options (e.g. counselling alone, nicotine replacement therapy) for people with cardiovascular disease who wish to stop smoking (see Who is it for). For people with no history of cardiovascular disease, advise them about a possible small increase in their absolute cardiovascular risk.¹⁰ Explain that this needs to be weighed up against the potential cardiovascular benefits of the medicine in helping them to quit (see Information for patients).^{10,11}

Advise patients to promptly report rash or swelling

Rare cases of life-threatening skin reactions including Stevens–Johnson syndrome and erythema multiforme have been reported in people taking varenicline.³ Hypersensitivity reactions including rare cases of life-threatening angioedema have also been reported.³ Tell patients to stop taking varenicline and to see a doctor at the first sign of rash, or if they experience swelling of the face, mouth, neck or extremities.³

Other safety considerations

Be aware of the following.

- ▶ Varenicline treatment withdrawal may cause increased irritability, urge to smoke, depression and sleep disturbances in up to 3% of people.³
- ▶ The safety of varenicline has not been established in pregnant or breastfeeding women or in people aged less than 18 years.³
- ▶ People taking varenicline experienced a weight gain of about 3 kg in clinical trials, which was similar to that seen in people taking placebo.^{4,5}
- ▶ Other adverse events reported in post-marketing use of varenicline include:
 - acute interstitial nephritis²⁹ and acute renal failure in people with pre-existing renal impairment³⁰ (See Reduce varenicline dose in renal disease)
 - acute hepatic injury in a man with existing liver disease³¹
 - proximal myopathy³²
 - triggering of pheochromocytoma crisis.³³

Reason for PBS listing

The Pharmaceutical Benefits Advisory Committee (PBAC) recommended the listing of a 12-week course of varenicline for smoking cessation on the basis of acceptable cost-effectiveness compared with bupropion.³⁴

The PBAC recommended a 12-week extension for people who successfully complete initial treatment based on an acceptable cost-effectiveness ratio compared with placebo.³⁵ The PBAC accepted that an additional 12 weeks of varenicline treatment has superior efficacy, but not safety, to that of placebo. Although the absolute difference in abstinence rates at 52 weeks with extended treatment versus placebo was small (about 7%), the PBAC considered the gain worth the cost when translated into extra Australians successfully quitting smoking.³⁶

Dosing issues

People should set a date to stop smoking. Start varenicline 1–2 weeks before their quit date.³ 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.

For people who successfully stop smoking at the end of 12 weeks, a further 12 weeks' therapy, continuing with 1 mg twice daily, is recommended to increase the chance of remaining abstinent at 1 year.

The initiation pack contains 11 × 0.5 mg, 14 × 1 mg and 28 × 1 mg varenicline tablets. The second prescription provides two boxes of 56 × 1 mg tablets. A third prescription (when indicated for weeks 13–24) provides one box of 56 × 1 mg tablets, with two repeats. 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.

Reduce varenicline dose in renal disease

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).³ 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.³

Information for patients

Provide advice on how to take varenicline, common side effects, and possible severe side effects.

Explain how to take varenicline

- ▶ Set a date to stop smoking and start varenicline 1–2 weeks before (to reduce craving and withdrawal symptoms).³
- ▶ Don't use nicotine-containing therapies while using varenicline; using nicotine replacement at the same time may cause nausea, headache, dyspepsia, fatigue and dizziness.³
- ▶ Follow the smoking-cessation program recommended by their health professional, as this can increase their chance of quitting for good. Advise them about additional smoking-cessation services available in their area and how to access them if necessary.

Advise about common side effects and concerns

- ▶ Varenicline frequently causes nausea that may settle over time. Advise patients to take varenicline with food and a full glass of water, which may help reduce nausea.³⁷ Ask them to tell their doctor if nausea is severe or prevents them from taking their medication.
- ▶ Varenicline can cause dizziness and sleepiness in some people. Advise them to be cautious when driving or operating machinery until they know how varenicline affects them.³
- ▶ At the end of varenicline treatment some people 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).³⁸ In clinical trials with varenicline, participants experienced a weight gain of about 3 kg.^{4,5}
- ▶ Varenicline is a relatively new medicine (available as a Pharmaceutical Benefit in Australia since January 2008) 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.

Advise about possible severe psychiatric, cardiovascular and skin effects

- ▶ Before prescribing, ask all patients about any history of psychiatric illness and suggest other smoking cessation options for anyone with a psychiatric illness or substance abuse disorder.⁷
- ▶ Discuss the possibility of mood changes and other psychiatric adverse effects with patients and their carers, including patients with no history of mental illness.³
- ▶ Advise patients to stop taking varenicline and to see their doctor as soon as possible if they experience an unusual or serious change in their mood or behaviour.^{24,37,39}
- ▶ Advise patients that varenicline may cause a small increase in risk of a cardiovascular event (e.g. heart attack). However, this needs to be weighed up against the potential cardiovascular benefits of the medicine in helping them to quit. Advise them to seek urgent medical attention if they experience new or worsening symptoms of cardiovascular disease (e.g. chest pain, shortness of breath or trouble breathing, pain in legs when walking).^{11,28}
- ▶ Advise patients to stop taking varenicline and see their doctor at the first sign of rash, swelling of the face, mouth, neck or extremities.³⁷

Discuss the Champix consumer medicine information (CMI) leaflet with the patient.



MEDICINE UPDATE

An NPS *Medicine Update* article 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 cessation programs call the Quitline on 137848 or visit: National Tobacco Campaign (www.quitnow.info.au).

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NPS RADAR articles may be updated when there is new evidence about safety or efficacy, or in case of regulatory or PBS listing changes.

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