Varenicline

Section: 24. Medicines for mental and behavioural disorders > 24.5. Medicines for disorders due to psychoactive substance use > 24.5.2. Medicines for nicotine use disorders

ATC codes: N07BA03

Indication	Nicotine dependence ICD11 code: 6C4A.2Z
INN	Varenicline
Medicine type	Chemical agent
List type	Core
Formulations	**Oral > Solid:** 0.5 mg ; 1 mg
EML status history	First added in 2021 (TRS 1035)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Main patents have expired but secondary patents might remain active in some jurisdictions. For more information on specific patents and license status for developing countries visit www.MedsPal.org Read more about patents.
Wikipedia	Varenicline
DrugBank	Varenicline

Expert Committee recommendation

The Expert Committee noted that smoking is a major public health threat worldwide and causes substantial health and economic harm, including different cancers. Currently, the EML only includes nicotine replacement therapy for smoking cessation (chewing gum and transdermal patches). The Expert Committee considered the evidence shown in the application that the pooled risk ratio for continuous or sustained abstinence at 6 months or longer for varenicline at standard dosage versus placebo was significant. Moreover, varenicline was also significantly better than bupropion for this outcome. The pooled risk ratio for abstinence at 24 weeks was also significantly higher for varenicline than nicotine replacement therapy. As regards the safety of varenicline, neuropsychiatric effects are a concern. Still, the latest evidence from a randomized trial does not support a link between varenicline and these disorders, although people with past or current psychiatric illness may be at slightly higher risk of experiencing neuropsychiatric events than people without these disorders. The Expert Committee was aware that smoking cessation interventions are among the most cost-effective public health interventions. Compared with other agents (bupropion and nicotine replacement therapy), the price of varenicline is higher and its use and availability in low- and middle-income countries are still limited. The Expert Committee noted that the availability of different treatment options may enhance procurement capacity, lower prices and increase affordability through competition. The Expert Committee also noted that no specialist training is required to prescribe or use the medicine. However, the success of medications for quitting smoking is improved when smokers are prepared to quit, and receive quitting advice, counselling and support from health care providers. The Expert Committee therefore noted that while the effectiveness of pharmacological interventions for smoking cessation is high, their

success is dependent on a concomitant behavioural education approach such as counselling. In many countries, especially in low- and middle-income countries, the use of this approach as well as the strengthening of tobacco control policies are still not optimal. The Expert Committee noted that varenicline was mentioned in the WHO Report on the Global Tobacco Epidemic 2019 as a non-nicotine pharmacological intervention to help people to quit smoking. Considering the body of evidence supporting the efficacy and tolerability of varenicline, the Expert Committee recommended the inclusion of varenicline for smoking cessation in the core list of the EML. However, considering the limited evidence on the affordability of varenicline in low- and middle-income countries, mechanisms to estimate its costs in these countries need to be established with ministries of health.

Background

Varenicline has not previously been evaluated for inclusion on the EML. Nicotine replacement therapy (NRT), as chewing gum or transdermal patch formulations, has been included on the EML since 2009. The Expert Committee recommended listing on the basis of the public health need, high-quality evidence of effectiveness, and acceptable safety and cost-effectiveness. Other formulations were not recommended for inclusion at the time because less evidence was available of comparative safety, effectiveness and cost in different populations (1).

Public health relevance

Smoking is a leading cause of preventable death and disease worldwide and is a major global public health challenge. WHO estimates there are more than 1.3 billion tobacco users worldwide and about 80% of them live in low- and middle-income countries. While the prevalence of smoking has been declining across all income groups and in almost every region throughout the world, the average global smoking rate is still unacceptably high (19.2%) and about 8 million people still die every year from smoking-related diseases (2,3). Furthermore, the global economic burden associated with smoking-attributable morbidity and mortality is substantial. One study estimated the global health care cost for smoking-related diseases at about US$ 467 billion, which is about 5.7% of total global expenditure on health care. When accounting for loss of productivity, the total economic burden of smoking is estimated at more than US$ 1 trillion a year (4). The causal relationship between smoking tobacco and numerous disease processes, including cardiovascular disease (CVD), many types of cancer and pulmonary disease, is well established (5). For example, it is estimated that adults who smoke 20 cigarettes a day increase their relative risk of an ischaemic event by more than 50% and of the 9.4 million deaths attributed to coronary heart disease worldwide, about 18% are caused by smoking (6–8). In addition, smokers are at a 15–30 times higher risk of developing lung cancer compared with people who have never smoked, and are four times more likely to develop bladder cancer than people who do not smoke (9,10). Smoking is also the leading cause of chronic obstructive pulmonary disease (COPD) and 73% of disease-related mortality in high-income countries is attributable to smoking (11,12). Taken together, people who smoke may on average have a 10-year shorter life expectancy than people who have never smoked (13). There are benefits to quitting smoking at almost any age, and people who successfully quit may significantly reduce their risk of developing or dying from smoking-related diseases. For example, 10 years after quitting smoking, the risk of developing lung cancer is 50% lower compared with people who continue to smoke; after 15 years of quitting, the risk of developing CVD is almost the same as someone who has never smoked. There are also short-term benefits to health that occur only weeks or months after stopping smoking, such as reduced frequency of cough and shortness of breath, as well as improved circulation and lung function (2,5). The most common cessation approach taken by people who smoke is to make an unaided quit attempt, also known as quitting, so-called, cold turkey; it is estimated that about 4–8% of unaided quit attempts are successful (2,5). Several well established guidelines backed by high-quality evidence consider the combination of behavioural support and pharmacotherapy as the most effective way to quit smoking in the short and long term (14,15). Although the efficacy of smoking cessation interventions varies, the combination of medication and behavioural support can as much as double a smoker’s chances of quitting; the provision of medication or behavioural support alone have both been found superior to an unaided quit attempt (2,14). The uptake of interventions is dependent on both availability (i.e. access and cost) and on a smoker’s preferences, which are likely to differ across social and cultural backgrounds. Therefore, the ability to offer a range of smoking cessation options is critical to facilitate maximum uptake and optimal treatment effectiveness (2).

Benefits

Two identically designed double-blind preauthorization clinical trials (A3051028 and A3051036) prospectively compared the efficacy of varenicline (1 mg twice daily), sustained release bupropion (150 mg twice daily) and placebo in smoking cessation (16,17). Participants received treatment for 12 weeks, followed by a 40-week non-treatment phase. Participants were provided with an educational booklet on smoking cessation and received up to 10 minutes of smoking cessation counselling at each weekly treatment visit. The primary endpoint of the two studies was the 4-week continuous abstinence rate confirmed by measurement of expired carbon monoxide (CO), from week 9 to week 12. At the primary endpoint, varenicline was shown to be statistically significantly superior to bupropion and placebo. After the 40-week non-treatment phase, a key secondary endpoint for both studies was the continuous abstinence rate at week 52. Continuous abstinence was defined as the proportion of all participants treated who did not smoke from week 9 to week 52 and did not have an exhaled CO measurement of > 10 ppm. The continuous abstinence rates during weeks 9–12 and 9–52 are shown Table 16. Table 16. Continuous abstinence during weeks 9–12 and 9–52 in preauthorization studies Across both studies during active treatment, participant-reported outcome measures showed that craving and withdrawal were significantly reduced in participants randomized to varenicline compared with placebo. Varenicline also significantly reduced positive reinforcing effects of smoking, which can perpetuate smoking behaviour, in people who smoked during treatment compared with placebo. Maintenance of abstinence An open-label maintenance of abstinence study (A3051035) assessed the benefit of an additional 12 weeks of varenicline therapy on maintenance of abstinence in 1927 participants (18). Participants received varenicline 1 mg twice daily for 12 weeks. Participants who stopped smoking by week 12 were then randomized to receive either varenicline (1 mg twice daily) or placebo for an additional 12 weeks for a total study duration of 52 weeks. The study showed the benefit of an additional 12 weeks of treatment with varenicline 1 mg twice daily for the maintenance of smoking cessation compared with receiving a placebo after the first 12 weeks. The odds of maintaining abstinence at week 24, i.e. with an additional 12 weeks of treatment with varenicline, were 2.47 times higher than if receiving a placebo ($P < 0.001$). Superiority to placebo for continuous abstinence was maintained through week 52 (odds ratio (OR) 1.35; $P = 0.013$). Flexible quit date The effect of varenicline 1 mg twice daily in a flexible participant-selected quit date setting was assessed in a double-blind, placebo-controlled study of 651 people (study A3051095) (19). Participants were randomized 3:1 to varenicline (n = 486) or placebo (n = 165) for 12 weeks, followed by 12 weeks of post-treatment follow-up. Participants were instructed to select a quit date after the initial week of dose titration and before the clinical visit at the end of week 5 of treatment. The rate of CO-confirmed abstinence during weeks 9 to 12 was 53.9% in participants treated with varenicline compared with 19.4% in participants treated with placebo (OR 6.03, 95% confidence interval (CI) 3.80 to 9.56). From week 9 to 24 the abstinence rate in the varenicline group was 35.2% compared with 12.7% in the placebo group (OR 4.45, 95% CI 2.62 to 7.55). Varenicline retreatment Varenicline was evaluated in a double-blind, placebo-controlled trial of 494 participants who had made a previous attempt to quit smoking with varenicline, and either did not succeed in quitting or relapsed after treatment (20). Participants were randomized 1:1 to varenicline 1 mg twice daily (n = 249) or placebo (n = 245) for 12 weeks of treatment and followed for up to 40 weeks after treatment. Participants included in the study had taken varenicline in the past in an attempt to stop smoking (for a total treatment duration of a minimum of 2 weeks), at least 3 months before entry into this study and had been smoking for at least 4 weeks. Participants treated with varenicline had an abstinence rate (CO-confirmed) of 45.0% during weeks 9 to 12, significantly higher than the 11.8% abstinence rate of participants treated with placebo (OR 7.08, 95% CI 4.34 to 11.55). From weeks 9 through 52, the abstinence rate of participants treated with varenicline was 20.1% compared with 3.3% in those treated with placebo (OR 9.00, 95% CI 3.97 to 20.41). Gradual quitting approach Varenicline was evaluated in a 52-week double-blind placebo-controlled study of 1510 participants who were not able or willing to quit smoking within 4 weeks but were willing to gradually reduce their smoking over a 12-week period before quitting (21). Participants were randomized to either varenicline 1 mg twice daily (n = 760) or placebo (n = 750) for 24 weeks and followed up after treatment through week 52. Participants were instructed to reduce the number of cigarettes smoked by at least 50% by the end of the first 4 weeks of treatment, followed by a further 50% reduction from week 4 to week 8 of treatment, with the goal of reaching complete abstinence by 12 weeks. After the initial 12-

week reduction phase, participants continued treatment for another 12 weeks. Participants treated with varenicline had a significantly higher rate of continuous abstinence than those given placebo at weeks 15 through 24 (32.1% versus 6.9%, respectively; OR 8.74, 95% CI 6.09 to 12.53) and weeks 21 through 52 (27.0% versus 9.9%; OR 4.02, 95% CI 2.94 to 5.50). Smokers with CVD Varenicline was evaluated in a randomized, double-blind, placebo-controlled study of 703 people with stable, documented CVD (other than or in addition to hypertension) that had been diagnosed for more than 2 months (A3051049) (22). Participants aged 35–75 years were randomized to varenicline 1 mg twice daily or placebo for a treatment period of 12 weeks and were then followed for 40 weeks after treatment. Participants treated with varenicline had a CO-confirmed abstinence rate of 47.3% during weeks 9 through 12, significantly higher than the 14.3% abstinence rate of participants treated with placebo (OR 6.05, 95% CI 4.13 to 8.86). From week 9 through 52, the abstinence rate of participants treated with varenicline was 19.8% compared with 7.4% in those treated with placebo (OR 3.19, 95% CI 1.97 to 5.18). Smokers with COPD Varenicline was evaluated in a randomized, double-blind, placebo-controlled study of 499 participants with mild to moderate COPD with postbronchodilator forced expiratory volume 1/forced vital capacity (FEV1/FVC) < 70% and FEV1 ≥ 50% of predicted normal value (23). Participants aged ≥ 35 years were randomized to varenicline 1 mg twice daily or placebo for a treatment period of 12 weeks and then were followed for 40 weeks after treatment. Participants treated with varenicline had a higher rate of CO-confirmed abstinence during weeks 9 through 12 than participants treated with placebo (42.3% versus 8.8%, respectively; OR 8.40, 95% CI 4.99 to 14.14) and from weeks 9 through 52 (18.6% versus 5.6%, respectively; OR 4.04, 95% CI 2.13 to 7.67). Smokers with major depressive disorder Varenicline was evaluated in a randomized, double-blind, placebo-controlled study of 525 participants with major depressive disorder without psychotic features who were on a stable dose of antidepressant treatment for at least 2 months and/or who had experienced a major depressive episode in the past 2 years and had been successfully treated (24). Participants aged 18–75 years were randomized to varenicline 1 mg twice daily or placebo for a treatment period of 12 weeks and then followed for 40 weeks after treatment. Participants treated with varenicline had a CO-confirmed abstinence rate of 35.9% during weeks 9 through 12, significantly higher than the 15.6% abstinence rate of participants treated with placebo (OR 3.35, 95% CI 2.16 to 5.21). From week 9 through 52, the abstinence rate of participants treated with varenicline was 20.3% compared with 10.4% in those treated with placebo (OR 2.36, 95% CI 1.40 to 3.98). Smokers with and without history of psychiatric disorders Varenicline was evaluated in a 24-week, double-blind, NRT (nicotine patch) and placebo-controlled, multicentre, parallel group study – the EAGLES (Evaluating Adverse Events in a Global Smoking Cessation Study) trial (25). The study was designed to assess the safety and efficacy of varenicline 1 mg twice daily and bupropion hydrochloride 150 mg twice daily for smoking cessation: the primary safety focus was estimating the occurrence of neuropsychiatric adverse events and the main efficacy objectives were measuring continuous abstinence for weeks 9 to 12 and 9 to 24 in participants with and without a diagnosis of a psychiatric condition. The primary comparisons were varenicline versus placebo and bupropion versus placebo. NRT was included as an active control and study drugs were given via a triple dummy design, i.e. all participants took three drugs, which were either one active plus two placebo or all three were placebo. This allowed active versus active treatment comparisons as well as active versus placebo comparisons. The duration of active treatment was 12 weeks, followed by a non-treatment follow-up phase of an additional 12 weeks. In both groups and overall, all active treatments showed significantly greater efficacy in smoking cessation compared with placebo as measured at both weeks 9 to 12 (Table 17) and 9 to 24 (Table 18). In addition, varenicline showed significantly greater efficacy compared with bupropion and compared with nicotine patch at both weeks 9 to 12 and 9 to 24. However, no significant differences in effectiveness were seen between bupropion and nicotine patch in either time period. Table 17. Treatment comparison for continuous abstinence from tobacco use in smokers with and without psychiatric disorders, weeks 9–12 Table 18. Treatment comparison for continuous abstinence from tobacco use in smokers with and without psychiatric disorders, weeks 9–24 Healthy adolescent smokers Varenicline was evaluated in a 12-week, randomized, double-blind, placebo-controlled, parallel group, dose ranging study with 40 weeks of follow-up in 312 healthy adolescent smokers aged 12–19 years (26). Participants were randomized 1:1:1 to either high-dose varenicline (1 mg twice daily or 0.5 mg twice daily for those weighing < 55 kg), low-dose varenicline (0.5 mg twice daily or 0.5 mg once daily for those weighing < 55 kg) or placebo. The study included a 12-week treatment period and a 40-week non-treatment follow-up period. All participants received < 10 minutes of age-appropriate cessation counselling at every study visit, in person or by telephone. The study did not meet the

primary endpoint of the cotinine-confirmed (urine) continuous abstinence rate from week 9 to week 12 in the overall study sample for either dose of varenicline compared with placebo. Analyses of secondary endpoints were consistent with the primary endpoint analysis. Results of a post hoc analysis of efficacy for a subset of participants 12–17 years were similar to those for the overall sample. Varenicline was well tolerated in this study population, with an adverse event profile similar to that observed in healthy adult smokers and no notable findings for neuropsychiatric adverse events.

Harms

Safety in randomized controlled studies Eight phase II and III studies, which were conducted in smokers who were otherwise generally healthy, supported the initial authorization of varenicline. The studies included a total of 5944 participants, with 3940 exposed to varenicline. In most of these studies the treatment period was 12 weeks while in one study it was 24 weeks and in another it was 52 weeks. Most of the studies included non-treatment follow-up to 1 year from start of treatment. The two phase III pivotal studies of varenicline (16,17), included 692 participants treated with varenicline, 669 participants treated with bupropion and 684 participants treated with placebo. The most common adverse events in the varenicline treatment group were nausea (28.8% varenicline, 9.9% bupropion, 9.1% placebo), headache (14.2% varenicline, 11.1% bupropion, 12.4% placebo), insomnia (14.2% varenicline, 21.5% bupropion, 12.6% placebo) and abnormal dreams (11.7% varenicline, 5.7% bupropion, 4.5% placebo). In most cases, nausea occurred early in the treatment, was mild to moderate in severity and did not result in discontinuation of treatment. The occurrence of nausea decreased with time on varenicline (27). Varenicline was studied in several postauthorization studies including a study on smokers with COPD (23), a study on generally healthy smokers who were allowed to select a flexible quit date between days 8 and 35 of treatment (19), a study of varenicline retreatment (20), a study on patients with stable CVD (22), a study on patients with stable schizophrenia or schizoaffective disorder (28), a study on patients with major depressive disorder (24), a postapproval safety outcome study on patients without or with a history of psychiatric disorder (EAGLES trial) specifically designed to assess the frequency of neuropsychiatric adverse events (25), and a study on smokers who used a gradual approach to quitting smoking (21). Postauthorization trials have also been conducted in specific countries or geographic regions, including Asia, Africa, the Middle East and South America (29–32). The safety profile of varenicline was generally consistent across pre- and postauthorization studies. Table 19 shows the common adverse events in six preauthorization phase II-III studies (2005 pooled studies) and 15 pre- and postauthorization phase II-IV studies (2010 pooled studies). Table 20 shows common adverse events for the EAGLES study overall. Across all studies the most common adverts events reported in participants treated with varenicline and reported in a greater proportion of participants treated with varenicline than placebo were nausea, headache, abnormal dreams and insomnia. Table 19. Most frequently reported treatment-related adverse events (by ≥ 5% of participants in any treatment group) in pooled study cohorts Table 20. Most frequently reported treatment-related adverse events (by ≥ 5% of participants in any treatment arm), EAGLES trial A 2016 Cochrane review and meta-analysis of placebo-controlled clinical trials of nicotine receptor partial agonists for smoking cessation included 39 trials involving varenicline treatment in 11 801 participants in a variety of populations and settings (35). The most frequent adverse events for smokers treated with varenicline was mild to moderate nausea, at rates between 24% and 29% in most studies. The other frequently reported adverse events included insomnia, abnormal dreams and headache. Meta-analyses of these four adverse events for varenicline versus placebo gave the following risk ratios (RRs) of: RR 3.27 (95% CI 3.00 to 3.55; 32 studies; 14 963 participants) for nausea; RR 2.12 (95% CI 1.88 to 2.38; 26 studies; 13 682 participants) for abnormal dreams; RR 1.49 (95% CI 1.35 to 1.65; 29 studies; 14 447 participants) for insomnia; and RR 1.17 (95% CI 1.07 to 1.29; 25 studies; 13 835 participants) for headache, with all differences being statistically significant. The percentage of subjects experiencing at least one all-causality serious adverse event was low and similar between the varenicline and placebo groups in the 15 pooled preauthorization studies (3.2% versus 3.1%, respectively) (33). The most common adverse events leading to permanent treatment discontinuation were nausea, insomnia, depressed mood and depression. In the EAGLES study, the percentages of participants with serious adverse events were similar across all treatment groups (1.9% varenicline, 2.4% bupropion, 2.3% NRT and 2.0% placebo) (34). The percentage of participants who discontinued treatment due to adverse events was also similar across treatment

groups (8.2% varenicline, 8.8% bupropion and 8.0% NRT) and higher than the placebo group (6.1%). Higher percentages of participants in the group with psychiatric disorders discontinued study treatment due to adverse events compared with the group without psychiatric disorders (Table 21) (25). Table 21. Adverse events leading to discontinuation of study treatment, EAGLES trial Neuropsychiatric safety The EAGLES trial was a randomized, double-blind, triple-dummy, active and placebo-controlled study requested by the US Food and Drug Administration and conducted by Pfizer. The study evaluated the neuropsychiatric safety and efficacy of varenicline (1 mg twice daily) and bupropion sustained release (SR) (150 mg twice daily) compared with placebo and NRT (nicotine patch: 21 mg a day with tapering) for smoking cessation in 8144 participants with and without a history of psychiatric disorders (25). The study was also a postauthorization safety study in the European Union. In each treatment arm, participants were divided into two groups – those without a psychiatric disorder and those with a current or past history of affective, anxiety, psychotic or personality disorders. The primary endpoint was a composite of moderate and/or severe adverse events comprising agitation, aggression, anxiety, delusions, depression, feeling abnormal, hallucinations, homicidal ideation, hostility, irritability, mania, panic, paranoia, psychosis, suicidal ideation, and suicidal behaviour and completed suicide. In the overall study population, varenicline was not associated with an increased incidence of clinically significant neuropsychiatric adverse events for the composite primary endpoint. In the group without psychiatric disorders, the incidence of adverse events that comprised the primary endpoint was similar for varenicline and placebo (1.3% and 2.4%, respectively). In group without psychiatric disorders, the incidence of adverse events in the composite endpoint was higher for each of the active treatments compared with placebo (varenicline 6.5%, bupropion 6.7%, nicotine patch 5.2% and placebo 4.9%). However, in the psychiatric cohort, the 95% CI for all risk differences for treatment relative to placebo included zero. One completed suicide was reported in the EAGLES study, which occurred in a participant treated with placebo in the group without psychiatric disorders. No completed suicides were reported in the group with psychiatric disorders. The frequency of suicidal ideation during the treatment period as well as during post-treatment follow-up was similar across the different treatments including placebo. Based on the Columbia-Suicide Severity Rating Scale, in the group without psychiatric disorders, ≤ 1% of participants across the different treatments reported suicidal ideation and/or behaviour during treatment and ≤ 30 days after treatment. However, in the group with psychiatric disorders, the percentages of participants reporting suicidal ideation and/or behaviour for the same time period were 3% for varenicline, 1% for bupropion, 2% for nicotine patch and 2% for placebo. Several meta-analyses of neuropsychiatric adverse events in clinical studies with varenicline have shown similar results to the EAGLES trial. A systematic review and meta-analysis of 39 trials (10 761 participants) assessed the risk of neuropsychiatric adverse events associated with varenicline (36). No increased risk was found for: aggression (OR 0.91, 95% CI 0.52 to 1.59); depression (OR 0.96, 95% CI 0.75 to 1.22); irritability (OR 0.98, 95% CI 0.81 to 1.17); suicidal ideation (OR 0.58, 95% CI 0.28 to 1.20); or suicide or suicide attempt (OR 1.67, 95% CI 0.33 to 8.57). Varenicline was associated with a reduced risk of anxiety compared with placebo (OR 0.75, 95% CI 0.61 to 0.93). However, the drug was associated with an increased risk of sleep-related adverse events, including insomnia (OR 1.56, 95% CI 1.36 to 1.78), abnormal dreams (OR 2.38, 95% CI 2.05 to 2.77) and fatigue (OR 1.28, 95% CI 1.06 to 1.55). The 2016 Cochrane review (that included the EAGLES trial), included a meta-analysis of neuropsychiatric serious adverse events (35). The RR for depression was 0.94 (95% CI 0.77 to 1.14; 36 studies; 16 189 participants) and the RR for suicidal ideation was 0.68 (95% CI 0.43 to 1.07; 24 studies; 11 193 participants), both with non-statistically significant lower rates in the varenicline groups compared with placebo. Overall, the data available show no evidence of an increased risk of clinically significant neuropsychiatric events with varenicline. Cardiovascular safety The risk for cardiovascular events in people taking varenicline has been studied in individual clinical trials as well as several meta-analyses. In a Pfizer randomized trial of 714 people with stable cardiovascular disease (22), the overall rate of cardiovascular events was low and all-cause and cardiovascular mortality was lower in people treated with varenicline than with placebo (0.3% versus 0.6%, respectively; difference −0.3% 95% CI, −1.3 to 0.7). However, non-fatal myocardial infarction and non-fatal stroke occurred more frequently in people treated with varenicline compared with people given a placebo (difference between groups: 1.1% and 0.3%, respectively), although the differences were not statistically significant. In a randomized trial of varenicline versus placebo in 302 participants with acute coronary syndrome (37), major adverse cardiovascular events (defined as death, myocardial infarction or hospitalization for unstable angina) were reported in 4.0% of participants in the varenicline group and 4.6% of participants in the placebo group.

Cardiovascular events were also prospectively collected and adjudicated during, and as part of, a 28-week non-treatment follow-up to the EAGLES study, providing a total of 52 weeks of safety data (38). This study found no evidence that varenicline increased the risk of cardiovascular adverse events. However, because of the relatively low number of events overall, the upper bounds of the 95% CIs for hazard ratios and risk differences do not entirely rule out an association. Meta-analyses of cardiovascular events in clinical trials on varenicline have produced inconsistent findings, with some analyses suggesting an increase in cardiovascular events with varenicline treatment (39,40) and others suggesting no effect of treatment with varenicline on cardiovascular events (41–43). Methodological differences, the size and duration of the studies, and the low number of cardiovascular events overall, likely contribute to the different results.

Cost / cost effectiveness

Overall, smoking cessation therapy is considered to be a cost–effective intervention (2). The benefits of smoking cessation on outcomes (BENESCO) model has been applied for various countries in Europe, South America, Asia and the USA. These analyses were generally conducted from the perspective of a health care payer using direct costs (drug acquisition costs, cost of a physician visit and brief counselling) and treatment-related costs for each morbidity. The model simulated a single quit attempt over a 1-year period and assessed the impact (i.e. cost associated with smoking cessation treatment and the development of smoking-attributable morbidity and mortality) over 2, 5, 10, 20, 50 years and/or a life-time (46). In several published evaluations, 12 weeks of therapy with varenicline was predicted to be a more cost-effective intervention from the perspective of a health care payer over a 20-year or life-time period than bupropion, NRT or unaided quitting attempts in Belgium (47), Colombia (48), China Hong Kong Special Administrative Region (49), Czechia (50), Finland (51), Germany (52), Mexico (53), Netherlands (54), Scotland (55), Spain (56), Sweden (57), United Kingdom (58) and USA (59). The results are relatively consistent across countries with different levels of economic development, however most of the assessments have taken place in high- and middle-income countries.

WHO guidelines

WHO treatment guidelines for smoking cessation therapies are not currently available. The 2019 WHO report on the global tobacco epidemic recommends offering help to quit tobacco use as one of the key measures in the MPOWER strategy (2). The report recognizes that both behavioural cessation support and nicotine-replacement and non-nicotine pharmacotherapies are effective in helping people to quit tobacco use. Combining both behavioural and pharmacotherapy interventions, however, is more effective and can double the chances of successfully quitting (44). The 2003 WHO policy recommendations on smoking cessation and treatment of tobacco dependence, note that a variety of behavioural and pharmacological therapies for smoking cessation have proved effective, but that no single approach should be emphasized to the exclusion of the others, because the therapies vary widely in their efficacy, acceptability, cost–effectiveness and their cost on an individual and population basis (45).

Availability

Varenicline has received regulatory approval in 116 countries globally. With patent expiry, generic versions of varenicline may soon become available.

1. The selection and use of essential medicines. Report of the WHO Expert Committee, 2009 (including the 16th WHO Model List of Essential Medicines and the 2nd WHO Model List of Essential Medicines for Children). Geneva: World Health Organization; 2009 (WHO Technical Report Series, No. 958; https://apps.who.int/iris/handle/10665/44287, accessed 30 March 2021).
2. WHO report on the global tobacco epidemic, 2019: offer help to quit tobacco use. Geneva: World Health Organization; 2019 (https://apps.who.int/iris/handle/10665/326043, accessed 30 March 2021).
3. WHO global report on trends in prevalence of tobacco smoking 2000–2025. Third edition. Geneva: World Health Organization; 2019 (https://apps.who.int/iris/handle/10665/330221, accessed 30 March 2021).
4. Goodchild M, Nargis N, Tursan d'Espaignet E. Global economic cost of smoking-attributable diseases. Tob Control. 2018;27(1):58–64.
5. Smoking cessation. A report of the Surgeon General. Atlanta, GA: US. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion,

Office on Smoking and Health; 2020 (https://www.hhs.gov/sites/default/files/2020-cessation-sgr-full-report.pdf, accessed 30 March 2021).
6. Morris PB, Ference BA, Jahangir E, Feldman DN, Ryan JJ, Bahrami H, et al. Cardiovascular effects of exposure to cigarette smoke and electronic cigarettes: clinical perspectives from the Prevention of Cardiovascular Disease Section Leadership Council and Early Career Councils of the American College of Cardiology. J Am Coll Cardiol. 2015;66(12):1378–91.
7. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2018;392(10159):1923–94.
8. Puig-Cotado F, Tursan d'Espaignet E, St Claire S, Bianco E, Bhatti L, Schotte K, et al. Tobacco and coronary heart disease: WHO tobacco knowledge summaries. Geneva: World Health Organization; 2020 (https://apps.who.int/iris/handle/10665/334325, accessed 15 October 2020).
9. Walser T, Cui X, Yanagawa J, Lee JM, Heinrich E, Lee G, et al. Smoking and lung cancer: the role of inflammation. Proc Am Thorac Soc. 2008;5(8):811–5.
10. Freedman ND, Silverman DT, Hollenbeck AR, Schatzkin A, Abnet CC. Association between smoking and risk of bladder cancer among men and women. JAMA. 2011;306(7):737–45.
11. Forey BA, Thornton AJ, Lee PN. Systematic review with meta-analysis of the epidemiological evidence relating smoking to COPD, chronic bronchitis and emphysema. BMC Pulm Med. 2011;11:36.
12. Mannino DM, Buist AS. Global burden of COPD: risk factors, prevalence, and future trends. Lancet. 2007;370(9589):765–73.
13. Smoking & tobacco use. Fast Facts. Atlanta, GA: Office on Smoking and Health (OSH), Centers for Disease Control and Prevention (https://www.cdc.gov/tobacco/data_statistics/fact_sheets/fast_facts/index.htm#diseases, accessed 15 October 2020).
14. Fiore M, Jaén CR, Baker TB, Bailey WC, Bennett G, Benowitz NL, et al. Tobacco Use and Dependence Guideline Panel. Treating tobacco use and dependence: 2008 update. Rockville, MD: US Department of Health and Human Services; 2008 (https://www.ncbi.nlm.nih.gov/books/NBK63952/, accessed 30 March 2021).
15. Stop smoking interventions and services. NICE guideline [NG92]. London: National institute for health and care excellence; 2018 (https://www.nice.org.uk/guidance/ng92, accessed 30 March 2021).
16. Gonzales D, Rennard SI, Nides M, Oncken C, Azoulay S, Billing CB, et al. Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. JAMA. 2006;296(1):47–55.
17. Jorenby DE, Hays JT, Rigotti NA, Azoulay S, Watsky EJ, Williams KE, et al. Efficacy of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. JAMA. 2006;296(1):56–63.
18. Tonstad S, Tønnesen P, Hajek P, Williams KE, Billing CB, Reeves KR. Effect of maintenance therapy with varenicline on smoking cessation: a randomized controlled trial. JAMA. 2006;296(1):64–71.
19. Rennard S, Hughes J, Cinciripini PM, Kralikova E, Raupach T, Arteaga C, et al. A randomized placebo-controlled trial of varenicline for smoking cessation allowing flexible quit dates. Nicotine Tob Res. 2012;14(3):343–50.
20. Gonzales D, Hajek P, Pliamm L, Nackaerts K, Tseng LJ, McRae TD, et al. Retreatment with varenicline for smoking cessation in smokers who have previously taken varenicline: a randomized, placebo-controlled trial. Clin Pharmacol Ther. 2014;96(3):390–6.
21. Ebbert JO, Hughes JR, West RJ, Rennard SI, Russ C, McRae TD, et al. Effect of varenicline on smoking cessation through smoking reduction: a randomized clinical trial. JAMA. 2015;313(7):687–94.
22. Rigotti NA, Pipe AL, Benowitz NL, Arteaga C, Garza D, Tonstad S. Efficacy and safety of varenicline for smoking cessation in patients with cardiovascular disease: a randomized trial. Circulation. 2010;121(2):221–9.
23. Tashkin DP, Rennard S, Hays JT, Ma W, Lawrence D, Lee TC. Effects of varenicline on smoking cessation in patients with mild to moderate COPD: a randomized controlled trial. Chest. 2011;139(3):591–9.
24. Anthenelli RM, Morris C, Ramey TS, Dubrava SJ, Tsilkos K, Russ C, et al. Effects of varenicline on smoking cessation in adults with stably treated current or past major depression: a randomized trial. Ann Intern Med. 2013;159(6):390–400.
25. Anthenelli RM, Benowitz NL, West R, St Aubin L, McRae T, Lawrence D, et al. Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): A double-blind, randomised, placebo-controlled clinical trial. Lancet. 2016;387(10037):2507–20.
26. Gray KM, Rubinstein ML, Prochaska JJ, DuBrava SJ, Holstein AR, Samuels L, et al. High-dose and low-dose varenicline for smoking cessation in adolescents: a randomised, placebo-controlled trial. Lancet Child Adolesc Health. 2020;4(11):837–45.
27. Nides M, Glover ED, Reus VI, Christen AG, Make BJ, Billing CB, Jr, et al. Varenicline versus bupropion SR or placebo for smoking cessation: a pooled analysis. Am J Health Behav. 2008;32(6):664–75.
28. Williams JM, Anthenelli RM, Morris CD, Treadow J, Thompson JR, Yunis C, et al. A randomized, double-blind, placebo-controlled study evaluating the safety and efficacy of varenicline for smoking cessation in patients with schizophrenia or schizoaffective disorder. J Clin Psychiatry. 2012;73(5):654–60.
29. Nakamura M, Oshima A, Fujimoto Y, Maruyama N, Ishibashi T, Reeves KR. Efficacy and tolerability of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, in a 12-week, randomized, placebo-controlled, dose-response study with 40-week follow-up for smoking cessation in Japanese smokers. Clin Ther. 2007;29(6):1040–56.
30. Tsai ST, Cho HJ, Cheng HS, Kim CH, Hsueh KC, Billing CB, Jr, et al. A randomized, placebo-controlled trial of varenicline, a selective alpha4beta2 nicotinic acetylcholine receptor partial agonist, as a new therapy for smoking cessation in Asian smokers. Clin Ther. 2007;29(6):1027–39.
31. Wang C, Xiao D, Chan KP, Pothirat C, Garza D, Davies S. Varenicline for smoking cessation: a placebo-controlled, randomized study. Respirology. 2009;14(3):384–92.
32. Bolliger CT, Issa JS, Posadas-Valay R, Safwat T, Abreu P, Correia EA, et al. Effects of varenicline in adult smokers: a multinational, 24-week, randomized, double-blind, placebo-controlled study. Clin Ther. 2011;33(4):465–77.
33. Approval package for Application Number: 021928Orig1s021. Silver Spring, MD: Center for Drug Evaluation and Research, Food and Drug Administration; 2011 (https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/021928

Orig1s021.pdf, accessed 30 March 2021).
34. CHANTIX® (varenicline). Tablets. 2016 FDA Advisory Committee Meeting Briefing Document. New York, NY: Pfizer; 2016 (https://www.fda.gov/media/100511/download, accessed 30 March 2021).
35. Cahill K, Lindson-Hawley N, Thomas KH, Fanshawe TR, Lancaster T. Nicotine receptor partial agonists for smoking cessation. Cochrane Database Syst Rev. 2016;2016(5):Cd006103.
36. Thomas KH, Martin RM, Knipe DW, Higgins JP, Gunnell D. Risk of neuropsychiatric adverse events associated with varenicline: systematic review and meta-analysis. BMJ. 2015;350:h1109.
37. Eisenberg MJ, Windle SB, Roy N, Old W, Grondin FR, Bata I, et al. Varenicline for smoking cessation in hospitalized patients with acute coronary syndrome. Circulation. 2016;133(1):21–30.
38. Benowitz NL, Pipe A, West R, Hays JT, Tonstad S, McRae T, et al. Cardiovascular Safety of varenicline, bupropion, and nicotine patch in smokers: a randomized clinical trial. JAMA internal medicine. 2018;178(5):622–31.
39. Singh S, Loke YK, Spangler JG, Furberg CD. Risk of serious adverse cardiovascular events associated with varenicline: a systematic review and meta-analysis. CMAJ. 2011;183(12):1359–66.
40. Ware JH, Vetrovec GW, Miller AB, Van Tosh A, Gaffney M, Yunis C, et al. Cardiovascular safety of varenicline: patient-level meta-analysis of randomized, blinded, placebo-controlled trials. Am J Ther. 2013;20(3):235–46.
41. Prochaska JJ, Hilton JF. Risk of cardiovascular serious adverse events associated with varenicline use for tobacco cessation: systematic review and meta-analysis. BMJ. 2012;344:e2856.
42. Mills EJ, Thorlund K, Eapen S, Wu P, Prochaska JJ. Cardiovascular events associated with smoking cessation pharmacotherapies: a network meta-analysis. Circulation. 2014;129(1):28–41.
43. Sterling LH, Windle SB, Filion KB, Touma L, Eisenberg MJ. Varenicline and Adverse cardiovascular events: a systematic review and meta-analysis of randomized controlled trials. J Am Heart Assoc. 2016;5(2):e002849.
44. West R, Raw M, McNeill A, Stead L, Aveyard P, Bitton J, et al. Health-care interventions to promote and assist tobacco cessation: a review of efficacy, effectiveness and affordability for use in national guideline development. Addiction. 2015;110(9):1388–403.
45. Policy recommendations on smoking cessation and treatment of tobacco dependence. Advancing tobacco control in the XXIst century. Geneva: World Health Organization; 2003 (https://apps.who.int/iris/handle/10665/42708, accessed 30 March 2021).
46. Keating GM, Lyseng-Williamson KA. Varenicline: a pharmacoeconomic review of its use as an aid to smoking cessation. Pharmacoeconomics. 2010;28(3):231–54.
47. Annemans L, Nackaerts K, Bartsch P, Prignot J, Marbaix S. Cost effectiveness of varenicline in Belgium, compared with bupropion, nicotine replacement therapy, brief counselling and unaided smoking cessation: a BENESCO Markov cost-effectiveness analysis. Clin Drug Investig. 2009;29(10):655–65.
48. Narvaez J, Alvis N, de La Hoz F, Orozco J, Porras A. An economic evaluation of a pharmacological intervention using varenicline as therapy for smoking cessation [abstract no. PRS16]. Value Health. 2009;12(3):A123.
49. Lee KK, Lee VWY, Chow DP. Cost effectiveness of varenicline compared with existing smoking cessation strategies in Hong Kong [abstract no. PRS16]. 12th Annual European Congress of the International Society for Pharmacoeconomics and Outcomes Research, 24–29 October 2009, Paris, France.
50. Skoupa J, Dolezal T, Hajek P, Kovár P. Long-term cost–effectiveness analysis of varenicline versus nicotine replacement therapy, bupropion, and unaided cessation for smoking cessation in the Czech Republic [abstract plus poster]. 10th Annual Meeting of the Society for Research on Nicotine and Tobacco Europe, 23–26 September 2008, Rome, Italy.
51. Linden K, Jormanainen V, Linna M, Sintonen H, Wilson K, Kotomaki T. Cost effectiveness of varenicline versus bupropion and unaided cessation for smoking cessation in a cohort of Finnish adult smokers. Curr Med Res Opin. 2010;26(3):549–60.
52. Rasch A, Greiner W. Gesundheitsökonomisches Modell der Raucherentwöhnung mit Vareniclin [Health economic model of smoking cessation with varenicline]. Suchtmedizin in Forschung und Praxis. 2009;11:47–55.
53. Mould-Quevedo JF, Contreras-Hernández I. Análisis coste-efectividad de vareniclina (Champix®) frente a los parches de nicotina en el tratamiento del tabaquismo en México [Cost-effectiveness analysis of varenicline (Champix®) versus nicotine patches in the treatment of smoking in Mexico]. PharmacoEconomics Spanish Research Articles. 2009;6(1):22–32.
54. Hoogendoorn M, Welsing P, Rutten-van Mölken MP. Cost-effectiveness of varenicline compared with bupropion, NRT, and nortriptyline for smoking cessation in the Netherlands. Curr Med Res Opin. 2008;24(1):51–61.
55. O'Regan CP, Baker CL, Marchant N. The cost-effectiveness of the novel prescription therapy varenicline in Scotland. [Abstract RPOS3-45 plus poster]. 13th Annual Meeting of the Society for the Research on Nicotine and Tobacco, 21–24 February 2007, Austin, Texas.
56. Fernández de Bobadilla Osorio J, Sánchez-Maestre C, Brosa Riestra M, Arroyo O, Sanz de Burgoa V, Wilson K. Análisis coste-efectividad de vareniclina (Champix) en el tratamiento del tabaquismo en España [Cost–effectiveness analysis of varenicline (Champix) for the treatment of smoking in Spain]. An Med Interna. 2008;25(7):342–8.
57. Bolin K, Mork AC, Willers S, Lindgren B. Varenicline as compared to bupropion in smoking-cessation therapy—cost-utility results for Sweden 2003. Respir Med. 2008;102(5):699–710.
58. Bolin K, Wilson K, Benhaddi H, de Nigris E, Marbaix S, Mork AC, et al. Cost-effectiveness of varenicline compared with nicotine patches for smoking cessation--results from four European countries. Eur J Public Health. 2009;19(6):650–4.
59. Howard P, Knight C, Boler A, Baker C. Cost-utility analysis of varenicline versus existing smoking cessation strategies using the BENESCO Simulation model: application to a population of US adult smokers. Pharmacoeconomics. 2008;26(6):497–511.

