

7.8 VARENICLINE, tablets, 500 microgram and 1 mg (as tartrate) (titration pack), tablets, 1 mg (as tartrate), Champix[®], Pfizer Australia Pty Ltd.

1 Purpose of Application

- 1.1 The major re-submission sought a change to the Authority Required listing of varenicline for smoking cessation. The re-submission requested a change to the NOTE to reduce the time to re-treatment with varenicline from 12 to 6 months.

2 Requested listing

- 2.1 The requested change to the listing for varenicline is indicated with strikethrough for text requested to be deleted and additional text underlined. Only the excerpt of the restriction where the change is requested is shown below.

NOTE:

A course of treatment with varenicline tartrate is 12 weeks or up to 24 weeks, if initial treatment of 12 weeks has been successful. ~~Only one course of 12 or up to 24 weeks of PBS subsidised varenicline tartrate will be authorised per year.~~ The period between commencing varenicline tartrate and bupropion hydrochloride or a further course of varenicline tartrate must be at least 6 months. No increased maximum quantities or repeats will be authorised. Clinical review is recommended within 2 to 3 weeks of the initial prescription being requested.

- 2.2 The submission did not seek to make any changes to the requested restriction in terms of:
- The indication and restriction category (aid to smoking cessation, Authority Required);
 - Price; or
 - Duration of therapy (12 weeks or up to 24 weeks, if remain abstinent in the first 12 weeks).
- 2.3 The re-submission claimed that varenicline is superior in comparative effectiveness to placebo, bupropion and nicotine replacement therapy (NRT). No comparative safety claims were made.

3 Background

- 3.1 Varenicline was TGA registered on 15 February 2007 as an aid for smoking cessation in adults over the age of 18 years.
- 3.2 The PBAC had considered this request once previously in November 2012.
- 3.3 The PBAC rejected the November 2012 submission on the basis that the efficacy and safety of varenicline in the population proposed for PBS listing could not be determined from the evidence presented (all trials enrolled varenicline-naïve patients), and hence that the cost effectiveness of varenicline in the proposed population was unknown.

4 Clinical place for the proposed therapy

- 4.1 Varenicline is indicated as an aid to tobacco smoking cessation for adults over the age of 18 years. Patients who have relapsed/not abstained during/after PBS-subsidised varenicline, nicotine replacement therapy (NRT) or bupropion treatment have to wait for a period of 12 months between commencement dates before restarting the same drug. Alternatively, 6 months after initiating treatment with varenicline, patients may commence bupropion or vice versa. There is no time restriction applicable to starting a course of NRT after a course of varenicline and/or bupropion.
- 4.2 The re-submission proposed that patients may have a second course of varenicline 6 months after attempting to cease smoking with varenicline, as an alternative to PBS-subsidised NRT or bupropion, or no treatment.

5 Comparator

- 5.1 As in the November 2012 submission, the re-submission nominated bupropion, NRT and placebo as the comparators. The PBAC considered these comparators were appropriate.

6 PBAC consideration of the evidence

Clinical trials

- 6.1 The re-submission presented four trials. Trial A3051139 was the pivotal trial which compared varenicline to placebo in a varenicline experienced population. Trials A3051028, A3051036 and A3051044 were presented as supportive evidence. The PBAC noted that Trial A3051139 was new evidence in this re-submission and the other three trials were presented in the previous submission. Details are presented in the table below.

Trial	Protocol title/ Publication title	Publication citation
Direct randomised trial		
Varenicline versus placebo		
Trial A3051139	Clinical study report A3051139. A phase 4 randomised, double-blind, placebo-controlled, multicentre study evaluating the efficacy and safety of re-treatment with varenicline in subjects who are currently smoking, and who have previously taken varenicline.	2013.
Varenicline vs bupropion and placebo		
Trial A3051028	Clinical study report A3051028. A twelve-week, double-blind, placebo-controlled, randomized, multicenter study with follow-up evaluating the safety and efficacy of varenicline tartrate (CP-526,555) in comparison to Zyban® for smoking cessation. Gonzales D, Rennard SI, Nides M, Oncken C, Azoulay S, Billing CB, Watsky EJ, Gong J, Williams KE, Reeves KR. Varenicline, an $\alpha 4\beta 2$ nicotinic acetylcholine receptor partial agonist, vs. sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial.	2005. <i>Journal of the American Medical Association.</i> 2006; 296(1):56-63.
A3051036	Clinical study report A3051036. A twelve-week,	2005

	double-blind, placebo-controlled, randomized, multicenter study with follow-up evaluating the safety and efficacy of varenicline tartrate (CP-526,555) in comparison to Zyban® for smoking cessation. Jorenby DE, Hays JT, Rigotti NA, Azoulay S, Watsky EJ, Williams KE, Billing CB, Gong J, Reeves KR. Efficacy of varenicline, an $\alpha 4\beta 2$ nicotinic acetylcholine receptor partial agonist, vs. placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial.	<i>Journal of the American Medical Association.</i> 2006;296(1):56-63.
Varenicline vs NRT		
A3051044	Clinical study report A3051044. An open label study that compares varenicline to transdermal nicotine patch for smoking cessation. Aubin H-J, Bobak A, Britton JR, Oncken C, Billing CB, Gong J, Williams KE and Reeves KR. Varenicline versus transdermal nicotine patch for smoking cessation: Results from a randomised, open-label trial.	2007 <i>Thorax</i> 2008;63(8):717-724.

Comparative effectiveness

- 6.2 The primary outcome of the trials presented was continuous quit rate (CQR) from weeks 9 to 12, with secondary outcomes including continuous abstinence rate (CAR) from week 9 to week 24 and CAR from week 9 to week 52.
- 6.3 The PBAC agreed with the submission that the most relevant patient outcome was the CAR from weeks 9 to 52. The results of the CAR over weeks 9-52 from the trials is presented in the table below.

Trial	Varenicline n/N (%)	Comparator n/N (%)	RR (95% CI)	RD (95% CI)	NNT (95% CI)
Varenicline versus placebo – varenicline naïve patients: presented in November 2012 submission					
A3051028	77/352 (21.9)	29/344 (8.4)	2.59 (1.74, 3.87)	0.13 (0.08, 0.19)	7 (12, 15)
A3051036	79/344 (23.0)	35/341 (10.3)	2.24 (1.55, 3.24)	0.13 (0.07, 0.18)	8 (5, 14)
A3051007/ A3051018 [^]	58/259 (22.4)	5/129 (3.9)	5.78 (2.38, 14.1)	0.19 (0.12, 0.25)	5 (4, 8)
Nakamura 2007	56/156 (35.9)	35/154 (22.7)	1.58 (1.10, 2.26)	0.13 (0.03, 0.23)	8 (4, 33)
Rigotti 2011	68/355 (19.2)	26/359 (7.2)	2.64 (1.72, 4.06)	0.12 (0.07, 0.17)	8 (6, 14)
Tashkin 2011	46/250 (18.4)	14/254 (5.5)	3.34 (1.88, 5.92)	0.13 (0.07, 0.18)	8 (5, 13)
Meta- analysis	394/1716 (23.0)	144/1581 (9.1)	2.50 (1.89, 3.31)	0.14 (0.11, 0.16)	7 (6, 9)
Varenicline versus placebo – varenicline experienced patients					
A3051139 [#]	██████████	██████████	██████████	██████████	██████████
██████████	██████████	██████████	██████████	██████████	██████████

Varenicline versus bupropion – varenicline naïve patients					
A3051028	77/352 (21.9)	54/329 (16.4)	1.33 (0.97, 1.82)	0.05 (0, 0.11)	NA
A3051036	79/344 (23.0)	51/342 (14.9)	1.54 (1.12, 2.12)	0.08 (0.02, 0.14)	12 (7, 45)
Meta-analysis	156/696 (22.4)	105/671 (15.6)	1.43 (1.14, 1.79)	0.07 (0.03, 0.11)	14 (9, 33)
Varenicline versus NRT – varenicline naïve patients					
A3051044	98/378 (25.9)	75/379 (19.8)	1.31 (1.01, 1.71)	0.06 (0.00, 0.12)	16 (8, 661)

Abbreviations: CAR = Continuous Abstinence Rate; NRT=nicotine replacement therapy (patch). NC = not calculated

Bold typography indicates statistically significant differences

Shaded cells represent new data presented in the re-submission, all other data was considered in the November 2012 submission

Source: Table B.6.5 pB-97 of the re-submission. *PSCR Table 3 (p2)*

results for All Randomised Population in Trial A3051139. Results are also based on the ITT population (all randomised subjects) in all the other trials.

^ The submission combines results from the 1.0mg bd non titrated (NT) varenicline treatment arm and 1.0mg bd titrated (TT) varenicline arm. All other studies use results from 1.0mg bd titrated varenicline arm only.

- 6.4 The PBAC noted there was a significantly higher rate of continuous abstinence over weeks 9-52 with varenicline compared to placebo, bupropion and NRT, in all the trials, with the exception of the varenicline versus bupropion Trial A3051028.
- 6.5 The PSCR presented sub-group analyses of treatment response according to time from the last quit attempt with varenicline to entry into trial A3051139. The PBAC noted that for the secondary endpoint of CAR weeks 9-52, treatment with varenicline in the [redacted] sub-group resulted in significantly higher CAR weeks 9-52 than placebo [redacted]
- 6.6 The PSCR also presented the results of a logistic regression model with Lag (time since last quit attempt) as a continuous variable. The results of testing for interaction between treatment group and time since last quit attempt are presented in the following table.

Effect	CAR Weeks 9-12	CAR Weeks 9-52
Lag by treatment interaction	[redacted]	[redacted]
Lag	[redacted]	[redacted]

Note: P-value from logistic regression model that included main effects for treatment and Lag and effect of interaction of treatment by lag.

- 6.7 The PBAC accepted that the results from this model demonstrated that there were no statistically significant differences by time since last quit attempt.

Comparative harms

- 6.8 The PBAC noted that the Core Data Sheet safety update presented by the re-submission was based on study A3051122 (Anthenelli 2013) in which varenicline naïve patients were treated for 12 weeks with varenicline. The PBAC considered the Core Data Sheet update was of limited applicability for the circumstances of the requested restriction permitting repeated varenicline exposure (up to 24 weeks for each treatment).

- 6.9 The PBAC was concerned about the safety of repeated and extended exposure to varenicline, in the context of documented neuropsychiatric and cardiovascular safety issues associated with varenicline. The PBAC considered that the Periodic Safety Update Report (PSUR) data provided in the submission did not provide clarity on the safety of repeated and extended exposure to varenicline.
- 6.10 The PBAC however considered that repeated courses of varenicline within a twelve month period were of acceptable safety based on the currently known safety profile of varenicline, which incorporates worldwide usage, and the information provided in the submission.
- 6.11 A summary of the comparative benefits and harms for varenicline versus placebo, bupropion or NRT is presented in the table below.

Outcome	N	RR (95%CI)	Event rate/100 patients/year		Increment
			Varenicline	Comparator ^a	
Benefits: CAR 9-52 weeks					
Meta-analysis Varenicline v placebo ^c	6 (3,297)	2.50 (1.89, 3.31)	23.0	9.1	0.14 (0.11, 0.16)
A3051139 Varenicline v placebo ^b	1 (498)	6.15 (2.98, 12.7)	19.9	3.2	0.17 (0.11, 0.22)
A3051028/3051036 Varenicline v bupropion ^c	2 (1,367)	1.43 (1.14, 1.79)	22.4	15.6	0.07 (0.03, 0.11)
A3051044 Varenicline v NRT ^c	1 (757)	1.31 (1.01, 1.71)	25.9	19.8	0.06 (0.00, 0.12)

^aplacebo, bupropion or NRT

^bvarenicline-experienced patients

^cvarenicline-naïve patients

Clinical claim

- 6.12 The re-submission claimed that varenicline is of superior efficacy to placebo, bupropion and NRT, and no worse in terms of safety to bupropion. The PBAC accepted these claims on the basis of the evidence presented. No claim was made with respect to comparative safety to placebo or NRT. The PBAC considered that varenicline is of inferior safety to placebo and NRT.

Economic analysis

- 6.13 The re-submission presented a cost-utility analysis and a cost effectiveness analysis. The economic model presented in the re-submission was the same as that presented in the November 2012 submission in terms of structure. Compared with the November 2012 submission, the re-submission's model had updated efficacy inputs (from Trial A3051139), updated inputs for raw population and mortality rates (Year 2007, AIHW 2010) and population attributable risk proportions (PAR%s) extrapolated to 2013. The model had a reference year of 2014.

6.14 A summary of the model structure and rationale is presented in the table below.

Component	Summary
Time horizon	20 years in the model base case versus 52 weeks in trial
Outcomes	CAR 9-52 weeks (from trials), LYG and QALYs
Comparator	PBN: A composite group comprising placebo (57.7%), bupropion (2.7%) and NRT (39.6%). The composition of the PBN group in the previous submission was placebo (92.6%), bupropion (1.8%) and NRT (5.6%).
Methods used to generate results	Cohort expected value analysis.
Health states	Three health states in the model: (i) smoker; (ii) ex-smoker and (iii) dead.
Cycle length	1 year
Transition probabilities	CAR for the first year in the model is derived from the trials (Table 2): <ul style="list-style-type: none"> • 19.92% for varenicline (Trial A3051139); • 3.24% for placebo (varenicline rate/RR varenicline v placebo from Trial A3051139); • 13.93% for bupropion (varenicline rate/RR varenicline v bupropion from the meta-analysis of Trials A3051028 and A3051036); • 15.21% for NRT (varenicline rate/RR varenicline v NRT from Trial A3051044). Assumed quit rate in years ≥ 2 and relapse rates are sourced from the literature, and mortality rates are derived from the literature and ABS data.
Utilities	Differential utility weights applied (age and sex specific) for smokers and ex-smokers, derived from the literature.

6.15 The PBAC agreed with the ESC that there were several issues in relation to the model structure and inputs including:

- the simple structure of the model had been previously accepted by PBAC but noted there were other published models, such as the BENESCO model of the cost-effectiveness of varenicline that were more comprehensive.
- In practice, non-pharmacological treatment is likely to include effective treatments such as cognitive behavioural therapy. The use of the trial placebo quit rate favours varenicline.
- The baseline quit rate of 5% per year is likely to be an overestimate. An Australian publication by Gartner et al 2009 found annual cessation rates ranging from 1.86% in 20-30 year old men to 5.93% in women over 51 years.

6.16 The PBAC noted the base case of the model only included intervention costs in the first year of use then modelled the benefits of the interventions for the subsequent years of the model. The PBAC noted that the results of the univariate sensitivity analyses indicated that the model was most sensitive to variations in the treatment efficacy of patients in the 'placebo' arm of the comparator group. The PBAC also noted that the model was sensitive to excess costs of smoking, comparator mix, assumed relapse rates, and the model duration. The PBAC considered the 20 year time horizon favoured varenicline.

6.17 The key drivers of the model are presented in the table below.

Description	Method/Value	Impact
Time horizon	20 years; assumed from 1 year trial duration	High, favours varenicline
Comparator mix	57.7% placebo, 2.7% bupropion, 39.6% NRT	High, favours varenicline

6.18 The results of the stepped economic evaluation are presented in the table below.

Step and component	Varenicline	PBN	Increment
Step 1: trial-based costs and outcomes – cohort of 251 patients			
Costs	████████	████████	████████
Number of quitters Week 9 to 52	██	████████	██
Incremental cost/additional quitter between week 9 to 52			████████
Step 2: trial results and premodelling (applying the trial results to the modelled cohort for one year) – cohort of 1,000 subjects			
Costs	████████	████████	████████
Proportion of quitters Week 9 to 52	████████	████████	████████
Number of quitters Week 9 to 52	██	██	██
Incremental cost/additional quitter between week 9 to 52			████████
Step 3: modelled evaluation extrapolating results of the pivotal trials to 20 years – cohort of 1,000 subjects			
Costs	████████	████████	████████
Discounted LYG over 20 years	████████	████████	████████
Incremental cost/extra life year gained			████████
Discounted QALY gained over 20 years	████████	████████	████████
Incremental cost/extra QALY			████████
Deaths over 20 years	████████	████████	████████
Incremental cost/extra death prevented			████████
Quitters over 20 years	████████	████████	████████
Incremental cost/extra quitter			████████

6.19 The PBAC noted that the re-submission estimated an ICER of less than \$15,000/QALY over 20 years (compared with less than \$15,000/QALY in the November 2012 submission), with differences stemming mostly from the assumed composition of the comparator group. The PBAC considered that the overall change to the listing of varenicline was of acceptable cost effectiveness. The PBAC noted that the ICER remained below \$20,000/QALY in the sensitivity analyses.

Estimated PBS usage & financial implications

6.20 The re-submission’s estimates of use and financial implications are presented in the table below.

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number of patients treated (initiation packs)	██████	██████	██████	██████	██████
Market share (% wishing to quit treated with varenicline 2 nd attempt)	██████	██████	██████	██████	██████
Varenicline patients: 1st attempt					
Initiation ^a	██████	██████	██████	██████	██████
Continuation ^b	██████	██████	██████	██████	██████
Completion (first prescription) ^c	██████	██████	██████	██████	██████
Completion (second and third prescription) ^d	██████	██████	██████	██████	██████
Varenicline patients: 2nd attempt					
Initiation ^a	██████	██████	██████	██████	██████
Continuation ^b	██████	██████	██████	██████	██████
Completion (first prescription) ^c	██████	██████	██████	██████	██████
Completion (second and third prescription) ^d	██████	██████	██████	██████	██████
Estimated net cost to PBS/RPBS/MBS					
Net cost to PBS	██████	██████	██████	██████	██████
Net cost to MBS	██████	██████	██████	██████	██████
Estimated total net cost					
Previous submission	██████	██████	██████	██████	██████

^aAssuming one script per patient as estimated by the re-submission.

^bAssuming 46% discontinue therapy (Day 28)

^cAssuming 5.7% receive additional 12 weeks of treatment

^dAssuming 7.8% discontinue therapy (additional 12 weeks of treatment)

6.21 The re-submission estimated the additional net cost to the PBS of the change to varenicline’s listing to be less than \$10 million in Year 5, with a net cost of \$30 million to \$60 million over the first five years of listing. The total net cost to the PBS for varenicline was estimated to be \$10 million to \$30 million in Year 5 and \$30 million to \$60 million over the first five years of listing.

6.22 The PBAC noted that the re-submission used a market share approach (based on PBS data for the initiation pack of varenicline) to estimate the PBS utilisation of varenicline. The previous submission took an epidemiological approach. The PBAC noted that the estimates were higher than the previous submission due to the assumption that more patients would undertake a second quit attempt with varenicline (ranging from 10,000 to 50,000 compared with 10,000 to 50,000 over years 1-5).

6.23 The PBAC noted that the estimates were most sensitive to the percentage of smokers that considered quitting using varenicline (second attempt) following an unsuccessful first attempt with varenicline.

7 PBAC Outcome

- 7.1 The PBAC recommended a change to the listing of varenicline (as tartrate) for smoking cessation to allow an additional course within a twelve month period for patients who have been unsuccessful in achieving abstinence from smoking during or after a course of PBS-subsidised varenicline. This recommendation was made on the basis of acceptable cost effectiveness to placebo, bupropion and nicotine replacement therapy (NRT).
- 7.2 The PBAC considered the comparators of bupropion, NRT and placebo were appropriate.
- 7.3 The re-submission presented four trials, with Trial A3051139, which compared varenicline to placebo in a varenicline experienced population, as the pivotal trial. The PBAC noted there was a significantly higher rate of continuous abstinence over weeks 9-52 with varenicline compared to placebo, bupropion and NRT, in all the trials, with the exception of the varenicline versus bupropion Trial A3051028.
- 7.4 The PSCR presented sub-group analyses of treatment response according to time from the last quit attempt with varenicline to entry into trial A3051139. The PBAC noted that for the secondary endpoint of CAR 9-52, treatment with varenicline in the [REDACTED] sub-group resulted in significantly higher CAR 9-52 than placebo [REDACTED]
- 7.5 [REDACTED] The PBAC accepted that the results from this model demonstrated that there were no statistically significant differences by time since last quit attempt.
- 7.6 The PBAC noted that the Core Data Sheet safety update presented by the re-submission was based on study A3051122 (Anthenelli 2013) in which varenicline naïve patients were treated for 12 weeks with varenicline. The PBAC considered the Core Data Sheet update was of limited applicability for the circumstances of the requested restriction permitting repeated varenicline exposure (up to 24 weeks for each treatment). The PBAC was concerned about the safety of repeated and extended exposure to varenicline, in the context of documented neuropsychiatric and cardiovascular safety issues associated with varenicline. The PBAC considered that the Periodic Safety Update Report (PSUR) data provided in the submission did not provide clarity on the safety of repeated and extended exposure to varenicline.
- 7.8 The PBAC considered that repeated courses of varenicline within a twelve month period were of acceptable safety based on the currently known safety profile of varenicline, which incorporates worldwide usage, and the information provided in the submission.
- 7.9 The PBAC accepted that varenicline is of superior efficacy to placebo, bupropion and NRT, and no worse in terms of safety to bupropion. The PBAC noted that no claim was made with respect to comparative safety to placebo or NRT. The PBAC considered that varenicline is of inferior safety to placebo and NRT.
- 7.10 The re-submission presented a cost-utility analysis and a cost effectiveness analysis. The economic model presented in the re-submission was the same as that presented in the November 2012 submission in terms of structure. Compared with the November 2012 submission, the re-submission's model had updated efficacy inputs (from Trial A3051139), updated inputs for raw population and mortality rates (Year

2007, AIHW 2010) and population attributable risk proportions extrapolated to 2013, and a reference year of 2014.

- 7.11 The PBAC considered the estimated ICER of less than \$15,000/QALY over 20 years and noted that overall the change to the listing of varenicline was of acceptable cost effectiveness. The PBAC noted that the ICER remained below \$20,000/QALY in the sensitivity analyses.
- 7.14 The PBAC noted the utilisation estimates were higher than the previous submission due to the assumption that more patients would undertake a second quit attempt with varenicline (ranging from 10,000 to 50,000 compared with 10,000 to 50,000 over years 1-5), however considered the estimates acceptable.

Outcome:

Recommended.

8 Recommended listing

- 8.1 To be finalised

Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

Sponsor's Comment

Pfizer Australia (the Sponsor) welcomes the PBAC recommendation to reduce the time between retreatment with varenicline from 12 to 6 months. The Sponsor believes that this change will result in a further reduction in the significant health and economic burden associated with smoking in Australia.