PUBLIC SUMMARY DOCUMENT
Product: Varenicline, tablets, 0.5 mg and 1 mg (as tartrate) (titration pack), tablets, 1 mg (as tartrate) Champix®
Sponsor: Pfizer Australia Pty Ltd
Date of PBAC Consideration: November 2012

1. Purpose of Application

The submission sought an amendment to the NOTE to the restriction of the current Authority Required listing to permit a further course of treatment in patients who did not cease smoking after a 12 week course of treatment or relapsed after a 12 or 24 week course of treatment, provided 6 months have elapsed between varenicline treatments.

2. Background

The PBAC had not previously considered this particular request.

Public summary documents for varenicline are available from the July 2007 and November 2009 PBAC meetings.

3. Registration Status

Varenicline was TGA registered on 15 February 2007 as an aid for smoking cessation in adults over the age of 18 years.

4. Listing Requested and PBAC's View

The requested changes to the existing listing are shown in ~~strikethrough~~ and *italics*. Varenicline is currently listed on the PBS, where initial treatment with varenicline is for 12 weeks, and for those who have abstained from smoking, an additional 12 weeks of treatment may be undertaken. The current listing allows for only one 12-24 week course of varenicline per year.

Authority Required

Commencement of short-term, sole PBS-subsidised, therapy as an aid to achieving abstinence in a patient who has indicated they are ready to cease smoking and:

(a) who has entered a comprehensive support and counselling program; or

(b) who is entering a comprehensive support and counselling program during the consultation at which this authority is requested.

Details of the program must be specified in the authority application.

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.

Authority Required
Continuation of short-term sole PBS-subsidised therapy as an aid to achieving abstinence in a patient who has previously been issued with an authority prescription for this drug and who is enrolled in a comprehensive support and counselling program.

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.

Authority Required
Completion of short-term sole PBS-subsidised therapy as an aid to achieving long-term abstinence after completion of an initial 12-week PBS-subsidised course in a patient who has ceased smoking, and who is enrolled in a comprehensive support and counselling program.

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.

5. Clinical Place for the Proposed Therapy

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 varenicline, nicotine replacement therapy (NRT) or bupropion treatment have to wait for a period of 12 months between commencement dates before restarting that drug. Alternatively, 6 months after supply of the varenicline initial prescription, patients may commence bupropion or vice versa and no time restriction is applicable for nicotine replacement therapy.

This submission proposed that patients may have a second course of varenicline instead of a course of PBS-subsided bupropion and/or NRT, non funded treatments or no treatment.

6. Comparator

The submission nominated bupropion, PBS subsidised nicotine replacement therapy (NRT) (transdermal patches) and placebo (no treatment) as the main comparators. The PBAC

considered these comparators were appropriate. The PBAC noted also that "no treatment" for placebo may include:

- nicotine replacement therapy: gum, lozenge, sublingual tablet, inhaler (all available without prescription);
- self-quit strategies: abrupt smoking cessation "Cold Turkey", provision of self-help materials; or
- group/individual counselling including cognitive and behaviour therapy, motivational counselling and other therapies. Some of these interventions are part of the "comprehensive support and counselling program" required in the current restriction for bupropion and varenicline.

7. Clinical Trials

The submission presented eleven trials; eight comparing varenicline and placebo, two three arm studies comparing varenicline with bupropion and placebo, and one comparing varenicline and NRT. The PBAC noted that the trial evidence presented was for smoking cessation in varenicline naïve patients. The PBAC considered that the evidence presented was not representative of the population in the proposed restriction and hence that the benefit of an additional smoking cessation attempt with a second varenicline course within six months compared to waiting another six months or using an alternative product listed on the PBS had not been demonstrated.

The table below details the published trials presented in the submission.

Trial ID/First Author	Protocol title/ Publication title	Publication citation
Varenicline vs Bupropion and Placebo		
A3051028 Gonzales D et al.	Varenicline, an alpha-4-beta-2 nicotinic acetylcholine receptor partial agonist, vs. sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial.	*Journal of the American Medical Association.* (2006); 296(1):56-63
A3051036 Jorenby DE et al.	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.	*Journal of the American Medical Association.* (2006); 296(1):56-63
Varenicline vs NRT		
A3051044 Aubin H-J et al.	Varenicline versus transdermal nicotine patch for smoking cessation: Results from a randomised, open-label trial.	*Thorax* (2008); 63(8):717-724
Varenicline vs Placebo		
A3051007/ A3051018^		

Oncken C et al.	Efficacy and safety of the novel selective nicotinic acetylcholine receptor partial agonist varenicline, for smoking cessation.	*Archives of Internal Medicine.* (2006);166:1571-7
Bolliger CT et al.	A Randomized Trial of Varenicline For Smoking Cessation in Latin America, Africa And The Middle East. Effects of Varenicline in Adult Smokers: A Multinational, 24-Week, Randomized, Double-Blind, Placebo-Controlled Study	*American Journal of Respiratory and Critical Care Medicine.* (2010);181:A2648 *Clinical Therapeutics.* (2011);33(4):465-477
Nakamura M et al.	Efficacy and Tolerability of Varenicline, an alpha-4-beta-2 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.	*Clinical Therapeutics*. (2007);29(6):1040-56
Rennard S et al.	A Randomized Placebo-Controlled Trial of Varenicline for Smoking Cessation Allowing Flexible Quit Dates.	*Nicotine & Tobacco Research* (2012);14(3):343-350
Rigotti NA et al.	Efficacy and Safety of Varenicline for Smoking Cessation in Patients with Cardiovascular Disease: A Randomized Trial A randomized Trial of Varenicline for Smoking Cessation in Patients with Cardiovascular Disease: Analysis of Efficacy by Baseline Characteristics.	*Circulation*. (2010);121:221-229 *Journal of the American College of Cardiology* (2009); 53(10), Supplement 1, Abs1048-67 *Circulation* (2010);122(2):AbsP929.
Tashkin DP et al.	Effects of Varenicline on Smoking Cessation in Patients With Mild to Moderate COPD: A Randomized Controlled Trial. Efficacy and safety of varenicline for smoking cessation in patients with mild to moderate COPD.	*Chest* (2011);139(3):591-599 *Chest*. *Conference: American College of Chest Physicians Annual Meeting.* 2009 San Diego, CA United States. Conference Publication: 136(4)
Tsai et al.	A Randomized, Placebo-Controlled Trial of Varenicline, a Selective α4β2 Nicotinic Acetylcholine Receptor Partial Agonist, as a New Therapy for Smoking Cessation in Asian Smokers.	*Clinical Therapeutics* (2007); 29(6):1027-39
Wang C et al.	Varenicline for smoking cessation: a placebo-controlled, randomized study.	*Respirology* (2009);14(3): 384–92

^ After completing the 12-week treatment period (Trial A3051007), subjects had the option of continuing in a non-treatment extension protocol (Trial A3051018) for an additional 40 weeks.

8. Results of Trials

Results of the trials (continuous abstinence week 9 to 52) for the meta-analysis of varenicline versus bupropion and placebo and the comparison of varenicline and NRT are presented in the table below.

Comparison*		Results Continuous Abstinence: Week 9-52	
		RR (95% CI)	RD (95% CI)
Varenicline	1.0 mg bd TT for 12 weeks (n=696)	1.43 (1.14, 1.79)	0.07 (0.03, 0.11)
Bupropion	150 mg bd TT for 10 weeks (n=671)		
Varenicline	1.0 mg bd TT for 12 weeks (n=378)	1.31 (1.01, 1.71)	0.06 (0.00, 0.12)
NRT	21 mg/day to 7 mg/day TT for 10 weeks (n=379)		
Varenicline	1.0 mg bd TT for 12 weeks (n=1716)	2.50 (1.89, 3.31)	0.14 (0.11, 0.16)
Placebo	(n=1581)		

Abbreviations: NRT = Nicotine Replacement Therapy (Transdermal Patch) TT = Titrated

In all of the trials, subjects were excluded on the basis of prior use of smoking cessation therapies over the previous month to six months. Most trials excluded patients with prior use of bupropion (excluding Nakamura 2007), and/or NRT (excluding Tsai 2007). Rennard 2012 and Tashkin 2011 were the only trials to specify varenicline in the exclusion criteria. Substantial variability was also noted in the reported number of previous attempts at smoking cessation and it is unclear what effect prior smoking cessation therapy may have on the efficacy of varenicline. As none of the trials examined the efficacy of varenicline in a retreatment scenario or the proposed shift for varenicline treatment cycles from twelve to six months for relapsed/non-abstinent smokers, the clinical data did not directly relate to the claim of the superior comparative effectiveness of varenicline over bupropion, NRT and placebo, or to the requested amendment to the restriction.

The PBAC noted that the safety outcomes reported in the submission were related to short term treatment with varenicline (12 weeks) and considered that the data was of limited applicability to the requested restriction which would permit repeated exposure to varenicline at six monthly cycles. The PBAC noted that the safety of longer term exposure to varenicline is unknown. The PBAC noted one twelve month safety study (Williams et al, 2007) which suggested no emergence of new adverse events; however this study excluded participants with cardiac disease, hypertension and using psychotropic medicines. In this context, the PBAC noted the psychiatric adverse effects known to be associated with treatment with varenicline, including depression, agitation, anxiety and aggression, and the post marketing reports of cardiovascular adverse events possibly associated with varenicline, including myocardial infarction and cerebrovascular accidents.

9. Clinical Claim

The submission described varenicline as superior in terms of comparative effectiveness and no worse in terms of comparative safety over bupropion.

The submission described varenicline as superior in terms of comparative effectiveness over NRT. The submission did not make any claim regarding safety.

The submission described varenicline as superior in terms of comparative effectiveness over placebo. The submission did not make any claim regarding safety.

For PBAC's views, see Recommendation and Reasons.

10. Economic Analysis

The submission presented a cost-utility analysis based on the claims of superior efficacy of varenicline to bupropion, NRT and placebo. The PBAC noted that the clinical evidence applied in the economic evaluation was for 12 weeks' treatment with varenicline. As the PBAC did not accept the clinical claims for the proposed PBS population made in the submission, the PBAC considered that the economic evaluation in turn did not inform on the cost effectiveness of varenicline in the proposed PBS population.

11. Estimated PBS Usage and Financial Implications

The submission estimated the additional net cost per year to the PBS to be less than $10 million in Year 5.

For PBAC's view, see Recommendation and Reasons.

12. Recommendation and Reasons

The submission nominated bupropion, PBS subsidised nicotine replacement therapy (NRT) (transdermal patches) and placebo (no treatment) as the main comparators. The PBAC considered these comparators were appropriate. The PBAC noted also that "no treatment" for placebo may include:

- nicotine replacement therapy: gum, lozenge, sublingual tablet, inhaler (all available without prescription);
- self-quit strategies: abrupt smoking cessation "Cold Turkey", provision of self-help materials; or
- group/individual counselling including cognitive and behaviour therapy, motivational counselling and other therapies. Some of these interventions are part of the "comprehensive support and counselling program" required in the current restriction for bupropion and varenicline.

The submission presented eleven trials; eight comparing varenicline and placebo (A3051007/A3051018, Bolliger 2011, Nakamura 2007, Rennard 2012, Rigotti 2010, Tashkin 2011, Tsai 2007 and Wang 2009), two three arm studies comparing varenicline with bupropion and placebo (A3051028 and A3051036), and one comparing varenicline and NRT (A3051044). The PBAC noted that the trial evidence presented was for smoking cessation in varenicline naïve patients. The PBAC considered that the evidence presented was not representative of the population in the proposed restriction and hence that the benefit of an additional smoking cessation attempt with a second varenicline course within six months compared to waiting another six months or using an alternative product listed on the PBS had not been demonstrated.

The PBAC noted that the safety outcomes reported in the submission were related to short term treatment with varenicline (12 weeks) and considered that the data was of limited applicability to the requested restriction which would permit repeated exposure to varenicline at six monthly cycles. The PBAC noted that the safety of longer term exposure to varenicline is unknown. The PBAC noted one twelve month safety study (Williams et al. 2007) which suggested no emergence of new adverse events; however this study excluded participants with cardiac disease, hypertension and using psychotropic medicines. In this context, the PBAC noted the psychiatric adverse effects known to be associated with treatment with varenicline, including depression, agitation, anxiety and aggression, and the post marketing reports of cardiovascular adverse events possibly associated with varenicline, including myocardial infarction and cerebrovascular accidents.

The PBAC did not accept the submission's claims that varenicline is superior in terms of comparative effectiveness and no worse in terms of comparative safety over bupropion, that varenicline is superior in terms of comparative effectiveness over NRT, nor that varenicline is superior in terms of comparative effectiveness over placebo in the extended population requested considering that the data presented in the submission was not representative of this population. The efficacy and safety of varenicline in the requested population is therefore unknown.

The submission presented a cost-utility analysis based on the claims of superior efficacy of varenicline to bupropion, NRT and placebo. The PBAC noted that the clinical evidence applied in the economic evaluation was for 12 weeks' treatment with varenicline. As the

PBAC did not accept the clinical claims for the proposed PBS population made in the submission, the PBAC considered that the economic evaluation in turn did not inform on the cost effectiveness of varenicline in the proposed PBS population.

The PBAC considered that the utilisation estimates presented in the submission were uncertain noting that the uptake rates and discontinuation rates for varenicline (first and second attempts), bupropion, PBS-NRT and other methods (including non-subsidised NRT) were assumed by the submission to be the same for the first five years of listing. The PBAC considered that the proposed extension to the listing of varenicline could result in changes to the utilisation rates of other therapies available on the PBS to aid smoking cessation (NRT, bupropion) and the use of non-PBS subsidised smoking cessation aids.

The PBAC therefore rejected the 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, and hence that the cost effectiveness of varenicline in the proposed population was unknown.

The PBAC noted that the literature review undertaken during evaluation of the submission identified a trial potentially relevant to the requested change to the listing for varenicline assessing the efficacy and safety of varenicline in smokers who have previously been treated with varenicline.[1] The PBAC further noted that this trial is being undertaken by the sponsor and is due for completion by November 2012. The PBAC considered that any re-submission should take the form of a major submission incorporating the results of this trial.

Recommendation:
Reject

13. 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.

14. Sponsor's Comment

The sponsor declined comment.

[1] ClinicalTrials.gov. A multi-national study to assess how effective and safe the smoking cessation medicine varenicline is in smokers who have already tried varenicline in the past as a prescription medicine from their usual healthcare provider. http://clinicaltrials.gov/ct2/show/NCT01244061 Last Accessed: 12 November 2012.