PUBLIC SUMMARY DOCUMENT
Product: Varenicline tartrate, tablet, 1 mg, Champix®
Sponsor: Pfizer Australia Pty Ltd
Date of PBAC Consideration: November 2009

1. Purpose of Application

To request the addition of a second continuing treatment restriction to the current authority required listing to allow a further 12 weeks of treatment for responders.

2. Background

At the July 2007 meeting, the PBAC recommended listing an authority required on the PBS of varenicline as a short-term treatment to aid smoking cessation on the basis of an acceptable cost-effectiveness compared with bupropion.

The PBAC noted the recommendation in the TGA approved Product Information that an additional 12 weeks treatment be undertaken by patients who have successfully stopped smoking during the first 12 weeks of treatment. However, the PBAC considered a further major submission would be required to justify this additional treatment period (which was not sought by the sponsor in its application).

Listing was effective from 1 January 2008.

3. Registration Status

Varenicline tartrate was registered on 15 February 2007 for the following indication:

- as an aid to smoking cessation for adults over the age of 18 years.

4. Listing Requested and PBAC's View

NOTE:
Only one course of PBS-subsidised varenicline tartrate will be authorised per year. The period between commencing a course of varenicline tartrate and bupropion hydrochloride must be at least 6 months. A course of treatment with varenicline tartrate is 12 weeks. No increased maximum quantities or repeats will be authorised. Clinical review is recommended within 2 to 3 weeks of the original prescription being requested.

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.

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.

Additional listing criteria are proposed as follows:
Authority Required
Continuation of short-term, sole PBS-subsidised, therapy as an aid to achieving long-term abstinence in a patient who has ceased smoking as a result of a previously issued authority prescription for this drug and who is enrolled in a comprehensive support and counselling program.

For PBAC's view see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Smoking related illnesses are a significant public health problem. Smoking and nicotine addiction are strongly interrelated and it is therefore important to treat them as such when attempting to reduce smoking prevalence. Varenicline may assist those patients who are ready to quit smoking to do so, together with appropriate support mechanisms.

6. Comparator

The submission nominated placebo as the main comparator, which was considered appropriate.

7. Clinical Trials

The submission presented one randomised, open-label trial (Trial A3051035) comparing varenicline 1mg twice a day with placebo in patients abstinent after an initial 12 weeks of treatment with varenicline. At the end of the 12 weeks open-label varenicline treatment 1236/1928 (64.1%) of patients remained abstinent from smoking and were randomised to either placebo or a further 12 weeks course of varenicline. This extended phase of the trial was double-blinded. Thereafter, participants continued into a non-treatment follow-up phase for an additional 28 weeks (for a total of 52 weeks in the trial). The primary outcome of the trial was carbon-monoxide confirmed continuous abstinence rate for weeks 13 to 24. The key secondary efficacy outcome was the continuous abstinence rate from week 13 through week 52.

The table below details the published trial presented in the submission:

Trial ID / First author	Protocol title / Publication title	Publication citation
A3051035 Tonstad S, et al.	Effect of maintenance therapy with varenicline on smoking cessation. A randomized controlled trial.	JAMA, 2006; 296(1):64-71.

8. Results of Trials

The primary outcome of Trial A3051035 (Continuous Abstinence Rate (CA) from Week 13 through Week 24) and the key secondary outcome relied upon in the

modelled economic evaluation (Continuous Abstinence Rate (CA) from Week 13 through Week 52) are summarised in the tables below.

The primary outcomes results of Continuous Abstinence Rate (CA) from Week 13 through Week 24 in Trial A3051035.

Varenicline n/N (%)	Placebo n/N (%)	OR (95% CI) p-value	Absolute difference RD± (95% CI) p-value	Relative difference RR (95% CI) p-value	NNT (95% CI)
425/602 (70.6%)	301/604 (49.8%)	2.47 (1.95, 3.15) p<0.0001	0.21 (0.15, 0.26) P<0.00001	1.42 (1.29, 1.56) P<0.00001	5 (4-7)

There were significantly more smokers who quit after 12 weeks of varenicline treatment, who maintained CA Week 13 to Week 24 than placebo controls during an additional 12 weeks of treatment with varenicline from (OR: 2.47 95% CI: 1.95, 3.15, p-value<0.0001).

The key secondary outcome results of Continuous Abstinence Rate from Week 13 through Week 52 in Trial A3051035.

Varenicline n/N (%)	Placebo n/N (%)	OR (95% CI) p-value	Absolute Difference RD ± (95% CI) p-value	Relative Difference RR (95% CI) p-value	NNT (95% CI)
265/602 (44.0%)	224/604 (37.1%)	1.35 (1.07, 1.70) P=0.0126	0.07 (0.01, 0.12) P=0.01	1.19 (1.03, 1.36) P=0.01	14 (8-71)

Abbreviations: NNT=number needed to treat

The proportion of patients maintaining complete abstinence from smoking from weeks 13 to 52 in the varenicline group who received an additional 12 week course after successful completion of an initial 12 week course, was 6.9 % higher than the placebo group.

The most commonly reported adverse events (AEs) during open label varenicline treatment were gastrointestinal (54.3%), psychiatric (35.9%) and nervous system disorders (23%), of which nausea (32.8%), insomnia (17.6%), abnormal dreams (14%) and headache (12.7%) were the most common AEs from these broad system classifications.

The submission provided additional data on potential safety concerns of varenicline beyond those identified in the clinical trials.

The submission acknowledged that from post-marketing data, neuropsychiatric AEs, not previously identified in clinical trials, are now recognised as a safety concern associated with varenicline. The submission discussed the causality of psychiatric events and the Sponsor's risk management plans.

For PBAC's view see Recommendation and Reasons.

9. Clinical Claim

The submission claimed an additional 12 weeks course of varenicline as superior in terms of comparative effectiveness and inferior in terms of comparative safety over placebo in patients who are abstinent from smoking after an initial 12 weeks course of varenicline. The PBAC accepted this claim.

10. Economic Analysis

The submission presented a stepped economic evaluation. The type of economic evaluation presented was a cost-utility analysis. The submission presented a decision analytic Markov model with time horizon of 19.77 years. The model compared two arms:

- no pharmacological treatment (placebo group)
- treatment with varenicline (varenicline group)

Three health states were possible in the model:

- smoker;
- ex-smoker;
- dead.

The perspective adopted for the analysis is that of the national healthcare system. Thus drug costs and direct medical costs associated with obtaining the drug are included in the analysis. In sensitivity analyses, the additional costs of direct medical treatment associated with a smoker, over and above those of an ex-smoker, were also included.

The outcomes generated by the modelled evaluation are incremental cost of varenicline versus placebo per additional life year gained and per additional QALY gained. These outcomes were translated from the Trial A3051035 outcome of Continuous Abstinence (CA) Rate Weeks 13 to 52.

The results of the sensitivity analyses indicate that the model is most sensitive to variations in treatment efficacy results of continued abstinence at Week 52. The incremental cost per extra QALY gained (males and females) was calculated to be less than $15,000.

For PBAC's view see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year was estimated to be between 10,000 – 50,000 in year 1 and decreasing in year 5. This estimation was considered to be underestimated.

Amended financial estimates in the Pre-Sub-Committee Response estimated the cost to the PBS to be greater than $10 million in the first year, decreasing to less than $10 million in year 5 of listing.

For PBAC's view see Recommendation and Reasons.

12. Recommendation and Reasons

The PBAC recommended the listing of varenicline tartrate tablets on the PBS be extended to make available a second 12 week course for patients who have successfully completed an initial 12 week course of varenicline, but require a further 12 week course to aid in maintaining abstinence, and who are enrolled in a comprehensive support and counselling program, on the basis of an acceptable cost effectiveness ratio. The PBAC accepted that varenicline is of superior efficacy and inferior safety to placebo.

The PBAC advised that it would be appropriate for the Pricing Authority to apply its usual methodology when considering the price for this extension to listing, which has substantial financial implications.

The PBAC noted the proportion of patients maintaining complete abstinence from smoking in trial A3051035 from weeks 13 to 52 in the varenicline group who received an additional 12 week course after successful completion of an initial 12 week course, was 6.9 % higher than the placebo group. The PBAC considered the absolute difference, although relatively small, was a significant gain when applied to the number of Australians currently smoking. The PBAC noted that trial results represent a best case scenario as the design of the trial maximises compliance, as the most responsive and motivated individuals were selected for the double-blind phase. In addition, education and counselling support were provided to patients in the trial at the start of the second 12 weeks of treatment, which also means that higher rates of abstinence are likely to have been observed in the trial than would be expected in clinical practice. The PBAC was concerned that patients with severe chronic obstructive pulmonary disease, cardiovascular disease, psychiatric illness or with a history of drug or alcohol abuse were excluded from the trial, but would be included in the PBS eligible population.

The PBAC considered the incremental cost of varenicline versus placebo per additional QALY which was less than $15,000 to be uncertain due to translation issues, but nevertheless acceptable.

The PBAC considered the utilisation estimates in the submission to be uncertain, however considered the estimates provided by the DUSC likely to be towards the upper end of expenditure.

The PBAC expressed the view that education of prescribers on the quality use of medicines (QUM) in smoking cessation is important and requested the National

Prescribing Service provide QUM education, emphasising the importance of counselling support, regarding this recommendation for varenicline.

Recommendation:
VARENICLINE
Amend NOTE to read:

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

VARENICLINE, tablet, 1 mg (as tartrate)
Amend the current restriction as follows:

Restriction: 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.

Maximum quantity: 112
Repeats: nil

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.

Maximum quantity: 56
Repeats: 2

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

Pfizer Australia (the Sponsor) welcomes the PBAC recommendation to list a further 12 weeks of varenicline (Champix) treatment for patients who are abstinent after the first 12 weeks of treatment in order to increase the likelihood of long term abstinence. The Sponsor believes the availability of the additional 12 weeks of Champix will provide a further reduction in the significant health and economic burden associated with smoking in Australia.