PUBLIC SUMMARY DOCUMENT

Product: NICOTINE, transdermal patch, releasing 15 mg per 16 hours, Nicorette®

Sponsor: Cancer Council Australia, National Heart Foundation of Australia, Australian Council on Smoking and Health and Quit Victoria.

Date of PBAC Consideration: March 2010

1. Purpose of Application

The submission sought to extend the current Pharmaceutical Benefits Scheme (PBS) listing for Aboriginal and Torres Strait Islanders to include patients in the general community that are either concession card holders or have a contraindication, precaution or adverse reaction that prevents them using other PBS listed smoking cessation pharmacotherapies.

2. Background

The PBAC had previously considered and rejected submissions for the listing of Nicorette® in December 2001 and June 2003. These two submissions were submitted by the Sponsor and the current submission was submitted by a consortium of not-for-profit agencies. Thus, any outstanding matters of concern to the PBAC would not have been available to the consortium and thus could not be addressed.

At the March 2008 meeting, the PBAC recommended an Authority required listing as the sole PBS-subsidised therapy for nicotine dependence in an Aboriginal or Torres Strait Islander person. The PBAC recommended only 2 courses of PBS-subsidised nicotine replacement therapy be authorised per year, noting that this population eschews oral aids for smoking cessation.

3. Registration Status

Nicorette patches are registered with the Therapeutic Goods Administration (TGA) for the treatment of tobacco dependence by relieving nicotine craving and withdrawal symptoms thus facilitating smoking cessation in smokers motivated to quit.

4. Listing Requested and PBAC's View

Authority required

Nicotine dependence in concessional patients, or patients for whom other smoking cessation pharmacotherapies should not be prescribed because of contraindications, precautions or adverse reactions, or an Aboriginal or a Torres Strait Islander person, as the sole PBS-subsidised therapy.

Note:

Only two courses of PBS-subsidised nicotine replacement therapy will be authorised per year. No applications for increased maximum quantity and/or repeats will be authorised. Benefit is improved if used in conjunction with a comprehensive support and counselling program.

The PBAC referred to the legal advice received from the Department stating that a pharmaceutical benefit cannot be listed on the PBS conditional on supply of that pharmaceutical benefit being restricted to persons of concession status. Therefore the PBAC considered the listing of nicotine patches for the total population. *See Recommendation and Reasons.*

5. Clinical place for the Proposed Therapy

Use as an alternative smoking cessation aid, particularly in patients for whom the current PBS-subsidised pharmacotherapies (bupropion and varenicline) are not suitable.

6. Comparator

The submission nominated varenicline as the main comparator because it is the product most likely to be replaced on the PBS. The PBAC agreed that varenicline is an appropriate comparator, but also as nicotine replacement therapy (NRT) is accepted as a first line pharmacotherapy for smoking cessation, then, an appropriate comparator was placebo for all patients. The PBAC considered that a comparison with bupropion was also appropriate.

7. Clinical Trials

The submission presented one randomised open-label trial comparing nicotine patch and varenicline in smokers motivated to quit smoking (Aubin et al. 2008). The dose regimens were:

- varenicline uptitrated to 1mg twice daily for 12 weeks or;
- transdermal nicotine replacement therapy (21 mg/day for 6 weeks, 14 mg/day for 2 weeks, then 7 mg/day for 2 weeks). This differs to the dose regimen proposed in the requested restriction of 15 mg/16 hour for 12 weeks.

The submission referred to results in a meta-analysis by Hughes et al. (2009) which included three trials (Goreka et al. 2003, Jorenby et al. 1999 and Uyar et al. 2007) comparing bupropion and nicotine transdermal patch (NTP). The results from a further trial (Piper et al. 2009) had since become available. During the evaluation a meta-analysis was conducted using all 4 trials.

The submission did not include a detailed comparison of NTP and placebo. However the submission referred to a published meta-analysis of randomised trials of NRT compared to placebo or to no treatment (Stead et al. 2008) in making the therapeutic claim that the comparative effectiveness of nicotine patch is superior to no pharmacological treatment.

The trials presented in the submission are shown below:

Trial ID / First author	Protocol title / Publication title	Publication citation
Aubin H-J et al. (2008)	Varenicline versus transdermal nicotine patch for smoking cessation: Results from a randomised, open-label trial.	*Thorax* 2008; 63(8): 717-724.

The dose regimens in the requested restriction and the key clinical trial were inconsistent with the TGA approved dose regimen for Nicorette® (in terms of patch strength, tapering and duration of therapy). The consortium pointed out that a Cochrane Collaboration review by Stead et al. concluded that 'Eight weeks of patch therapy is as effective as longer courses and there is no evidence that tapered therapy is better than abrupt withdrawal'. Nonetheless the consortium encouraged the PBAC to view favourably any applications to have additional strengths of nicotine patch listed and thereby enable tapering dosage where preferred by prescribers or patients.

Overall, the PBAC considered that while the claim of equivalence between dose regimens is uncertain, that based on the Cochrane review (Stead et al. 2008) any difference in efficacy between the different treatment regimens was likely to be small.

8. Results of Trials

The primary outcome was continuous abstinence rate (CAR) for the last 4 weeks of 12 weeks treatment. Secondary outcomes included CAR from the last 4 weeks of treatment through weeks 24 and 52, and measures of craving, withdrawal and smoking cessation.

NTP versus varenicline

The key results of the NTP versus varenicline comparison (based on Aubin et al. 2008) are summarised in the table below:

Outcome	NTP n/N (%)	Varenicline n/N (%)	OR (95% CI)[a] NTP v varenicline	RR (95% CI) NTP v varenicline
Primary analysis set: all randomised and treated patients				
CAR in last 4 weeks of treatment[b]	160/370 (42.3)	210/376 (55.9)	**0.60 (0.45, 0.80)**	**0.77 (0.67, 0.90)**
CAR at 24 weeks	101/370 (27.3)	122/376 (32.4)	0.78 (0.57, 1.07)	0.84 (0.67, 1.05)
CAR at 52 weeks	75/370 (20.3)	98/376 (26.1)	0.72 (0.51, 1.02)	0.78 (0.60, 1.01)
ITT: all randomised patients				
CAR in last 4 weeks of treatment[c]	160/379 (42.2)	210/378 (55.6)	**0.58 (0.44, 0.78)**	**0.76 (0.66, 0.88)**
CAR at 24 weeks	101/379 (26.6)	122/378 (32.2)	0.76 (0.56, 1.04)	0.83 (0.66, 1.03)
CAR at 52 weeks	75/379 (19.8)	98/378 (25.9)	**0.70 (0.50, 0.99)**	**0.76 (0.59, 0.99)**

[a] *estimated during the evaluation using Review Manager 5*

[b] primary outcome in the trial: weeks 8-11 for NTP and weeks 9-12 for varenicline

[c] weeks 8-11 for NTP and weeks 9-12 for varenicline

Bold typography indicates statistically significant differences

The PBAC noted that Aubin et al. (2008) reported a statistically significantly greater continuous abstinence rate, the primary outcome, for varenicline in the last 4 weeks of 12 weeks of treatment in each of the per protocol (PP) and intention to treat (ITT) populations. The PBAC also noted that although there was no statistical difference between the continuous abstinence rates of nicotine patches and varenicline at 24 weeks in both the PP and ITT populations, and at 52 weeks in the PP population, there was a statistically significant difference in favour of varenicline in the ITT population at 52 weeks. The Committee also noted that these were secondary outcomes of the trial and that the trial may not have been powered for these endpoints. The PBAC considered that this evidence was insufficient to support the submission's claim of non-inferiority of nicotine patches to varenicline.

The consortium argued that the CARs at 24 weeks and 52 weeks were the patient-relevant outcomes.

NTP versus bupropion

The PBAC noted that a meta-analysis of four trials (Gorecka et al. 2003, Jorenby et al. 1999, Uyar et al. 2007, Piper et al. 2009) conducted during the evaluation showed no significant difference between nicotine patches and bupropion and considered this supported non-inferiority of nicotine patches to bupropion for sustained abstinence at 6 months or greater.

NTP versus placebo

The submission presented no evidence to inform the comparison of NTP versus placebo and only provided a therapeutic conclusion based on the results reported in the Stead et al. (2008) meta-analysis: that the improvement in smoking cessation rate with nicotine patches compared with no NRT is statistically significant (risk ratio was 1.51 (95% CI: 1.35, 1.70)) for abstinence at 12 months. None of the placebo controlled trials included in the meta-analysis reported by Stead et al. (2008) utilised the NTP dosing regimen specified in the requested restriction, nor were any of the studies likely to have been conducted in patients for whom other smoking cessation pharmacotherapies should not be prescribed because of contraindications, precautions or adverse reactions.

The PBAC noted the Cochrane review (Stead et al. 2008) presented in the submission to support the claim of superiority of nicotine patches to placebo. For the outcome of sustained abstinence at 12 months the meta-analysis reported a statistically significant result favouring nicotine patches over placebo (risk ratio 1.51), however the PBAC noted that none of the trials in the meta-analysis included the dosage regimen requested in the submission. The Committee also noted that the same review suggested that such differences, including the use of different strength patches such as 21 mg for 24 hours or 15 mg for 16 hours, and gradual tapering compared with abrupt withdrawal, are likely to result in minimal changes in clinical outcomes.

The submission did not provide a quantitative analysis of the comparative safety of either the NTP versus varenicline or the NTP versus placebo comparison. The adverse events reported in the direct randomised trial of NTP versus varenicline reported by Aubin et al. (2008) were extracted during the evaluation and are presented in the table below:

Adverse event	**NTP N=370 n (%)**	**Varenicline N=376 n (%)**	**RR (95% CI)[a]**
Any adverse event	260 (70.3)	319 (84.8)	**0.83 (0.77, 0.90)**
Treatment discontinuation due to AE[b]	16 (4.3)	30 (8.0)	**0.54 (0.30, 0.98)**
Dose reductions or temporary withdrawal from study medication	25 (6.8)	44 (11.7)	**0.58 (0.36, 0.92)**
Deaths	0 (0.0)	0 (0.0)	NC
Serious AEs	8[c] (2.2)	2[d] (0.5)	4.06 (0.87, 19.01)
Severe AEs	27 (7.3)	37 (9.8)	0.74 (0.46, 1.19)
Nausea	0 (0.0)	7 (1.9)	0.07 (0.00, 1.18)
Insomnia	1 (<1.0)	5 (1.3)	0.20 (0.02, 1.73)
Headache	0 (0.0)	5 (1.3)	0.09 (0.01, 1.66)
Most frequent AEs			
Nausea	36 (9.7)	140 (37.2)	**0.26 (0.19, 0.37)**
Insomnia	71 (19.2)	80 (21.3)	0.90 (0.68, 1.20)
Headache	36 (9.7)	72 (19.1)	**0.51 (0.35, 0.74)**
Abnormal dreams	31 (8.4)	44 (11.7)	0.72 (0.46, 1.11)
Constipation	9 (2.4)	31 (8.2)	**0.30 (0.14, 0.61)**
Dizziness	13 (3.5)	28 (7.4)	**0.47 (0.25, 0.90)**
Disturbance in attention	5 (1.4)	24 (6.4)	**0.21 (0.08, 0.55)**
Vomiting	4 (1.1)	23 (6.1)	**0.18 (0.06, 0.51)**
Diarrhoea	10 (2.7)	22 (5.9)	**0.46 (0.22, 0.96)**
Flatulence	5 (1.4)	22 (5.9)	**0.23 (0.09, 0.60)**
Dysgeusia	4 (1.1)	22 (5.9)	**0.18 (0.06, 0.53)**
Abdominal pain (upper)	4 (1.1)	21 (5.6)	**0.19 (0.07, 0.56)**
Fatigue	9 (2.4)	21 (5.6)	**0.44 (0.20, 0.94)**

NTP=nicotine transdermal patch, AE=adverse event, RR=relative risk, CI=confidence interval, NC=not calculable.

[a] estimated during the evaluation using Review Manager 5

[b] most frequent AE leading to adverse event was nausea NTP=0.8 %, varenicline=2.1%, no other AE resulted in treatment discontinuation in > 1 % of the population

[c] bile duct cancer and sepsis (n=1), gastrointestinal bleeding (n=1), myocardial infarction (n=2), salivary gland tumour (n=1), chest pain (n=2), worsening of existing knee trauma (n=1) – none attributable to NTP

[d] depression (n=1) and constipation (n=1) – depression attributable to varenicline

Bold typography indicates statistically significant differences

Numerous statistically significant differences in the incidence of adverse events were observed between NTP and varenicline, however in each instance, the events were less likely to occur in patients treated with NTP compared with varenicline.

The submission provided an analysis of the TGA-approved Product Information documents for nicotine patch, bupropion and varenicline. This analysis noted that bupropion and varenicline are either contraindicated or precautions are advised for certain patients (for example those with seizure disorders or serious psychiatric illnesses) but that nicotine patch is not contraindicated for these patients.

The PBAC considered that nicotine patches are less toxic than varenicline or bupropion. The Committee noted the adverse events comparison of nicotine patches and varenicline from Aubin et al. (2008) extracted during the evaluation, showing statistically significant lower rates of adverse reactions for nicotine patches for the majority of the most frequently reported adverse events in the trial. The PBAC noted that the Hughes et al. (2009) meta-analysis did not report on the comparative safety of nicotine patches versus bupropion, however in Piper et al. (2009) there was a higher incidence of skin irritations with nicotine patches but overall nicotine patches were less toxic than bupropion.

9. Clinical Claim

The submission stated that the comparative effectiveness of nicotine transdermal patches to varenicline is uncertain and that nicotine transdermal patches may be non-inferior or inferior and that the comparative safety of nicotine transdermal patch relative to varenicline is superior.

The submission also concluded that the comparative effectiveness of nicotine patch relative to no pharmacological treatment is ‘superior’.

Based on the totality of the evidence, the PBAC considered that the claim of non-inferiority of nicotine patches to varenicline to be uncertain with the evidence suggesting that varenicline is more effective and more toxic, that the evidence supports nicotine patches being more effective and less safe than placebo, and that nicotine patches are of non-inferior efficacy to bupropion and of superior safety.

10. Economic Analysis

The submission provided a cost-analysis comparing NTP and varenicline, assuming equi-effective doses of 12 weeks of 15 mg/16 hour NTP therapy as being equivalent to 12 weeks of varenicline therapy.

The recent PBAC recommendation to allow for an additional 12 weeks of treatment with varenicline in patients who successfully abstain from smoking following the initial 12

week treatment period is likely to have made NTP even less costly and less effective than varenicline.

The PBAC noted that the cost-analysis did not take into account the lower effectiveness of nicotine patches in comparison to varenicline in Aubin et al. (2008). However the cost-analysis also did not include any indirect costs such as those associated with the management of adverse effects to varenicline which the PBAC considered are likely to be greater for varenicline than for nicotine patches. The PBAC hence considered the evidence indicated that nicotine patches are less effective, of superior safety and less expensive than varenicline based on the evidence presented.

The PBAC also noted that the price requested in the submission for nicotine patches is less than that for a PBS course of bupropion. Based on the meta-analysis conducted during the evaluation the PBAC considered that nicotine patches are non-inferior to bupropion. The PBAC also considered that bupropion is more toxic than nicotine patches. The Committee noted that if other costs were also taken into account, including GP consultations for the management of adverse events associated with bupropion, this would favourably affect the cost effectiveness of nicotine patches.

11. Estimated PBS Usage and Financial Implications

The submission estimated the number of patients using PBS subsidised NRT to be greater than 200,000 patients in all years of listing.

The net financial cost/year to the PBS was estimated during the evaluation to be a cost saving of less than $10 million in all years of listing.

The PBAC considered that the submission's estimate of the utilisation of nicotine patches and overall cost to Government is highly uncertain, and substantially underestimated. *See Recommendations and Reasons.*

12. Recommendation and Reasons

The PBAC recommended the listing of nicotine transdermal patches on the PBS as an Authority required listing as an aid to cessation of smoking in patients who have entered or are entering a comprehensive support and counselling program in the context of a public health priority area, noting that reduction of chronic disease caused by smoking is one of the key focuses of the national health taskforce on prevention. The PBAC recommended the listing of nicotine transdermal patches at the price requested in the submission on the basis of (a) non-inferior efficacy, superior safety and lower cost compared to bupropion, and (b) uncertain and possibly inferior efficacy, superior safety and lower cost compared to varenicline. The PBAC recommended that the listing of nicotine patches be limited a maximum of 12 weeks treatment in a 12 month period.

The PBAC referred to the legal advice received from the Department stating that a pharmaceutical benefit cannot be listed on the PBS conditional on supply of that pharmaceutical benefit being restricted to persons of concession status. Therefore the PBAC considered the listing of nicotine patches for the total population.

The submission presented an open label randomised trial comparing nicotine transdermal patch and varenicline in smokers motivated to quit smoking (Aubin et al. 2008). The PBAC noted that the trial reported a statistically significantly greater continuous

abstinence rate, the primary outcome, for varenicline in the last 4 weeks of 12 weeks of treatment in each of the per protocol (PP) and intention to treat (ITT) populations. The PBAC also noted that although there was no statistical difference between the continuous abstinence rates of nicotine patches and varenicline at 24 weeks in both the PP and ITT populations, and at 52 weeks in the PP population, there was a statistically significant difference in favour of varenicline in the ITT population at 52 weeks. The Committee also noted that these were secondary outcomes of the trial and that the trial may not have been powered for these endpoints. The PBAC considered that this evidence was insufficient to support the submission's claim of non-inferiority of nicotine patches to varenicline.

The PBAC noted the Cochrane review (Stead et. al. 2008) presented in the submission to support the claim of superiority of nicotine patches to placebo. For the outcome of sustained abstinence at 12 months the meta-analysis reported a statistically significant result favouring nicotine patches over placebo (risk ratio 1.51), however the PBAC noted that none of the trials in the meta-analysis included the dosage regimen requested in the submission. The Committee also noted that the same review suggested that such differences, including the use of different strength patches such as 21 mg for 24 hours or 15 mg for 16 hours, and gradual tapering compared with abrupt withdrawal, are likely to result in minimal changes in clinical outcomes.

The PBAC noted that a meta-analysis of four trials (Gorecka et al. 2003, Jorenby et al. 1999, Uyar et al. 2007, Piper et al. 2009) conducted during the evaluation showed no significant difference between nicotine patches and bupropion and considered this supported non-inferiority of nicotine patches to bupropion for sustained abstinence at 6 months or greater.

In terms of safety, the PBAC considered that nicotine patches are less toxic than varenicline or bupropion. The Committee noted the adverse events comparison of nicotine patches and varenicline from Aubin et al. (2008), extracted during the evaluation, showing statistically significant lower rates of adverse reactions for nicotine patches for the majority of the most frequently reported adverse events in the trial. The PBAC noted that the Hughes et al. (2009) meta-analysis did not report on the comparative safety of nicotine patches versus bupropion, however in Piper et al. (2009) there was a higher incidence of skin irritations with nicotine patches but overall nicotine patches was less toxic than bupropion.

The submission presented a cost-analysis comparing 12 weeks of treatment with nicotine patches, at the current price, and varenicline. The PBAC noted that the cost-analysis did not take into account the lower effectiveness of nicotine patches in comparison to varenicline in Aubin et al. (2008). However the cost-analysis also did not include any indirect costs such as those associated with the management of adverse effects to varenicline which the PBAC considered are likely to be greater for varenicline than for nicotine patches. The PBAC hence considered the evidence indicated that nicotine patches are less effective, of superior safety and less expensive than varenicline based on the evidence presented.

The PBAC also noted that the price requested in the submission for nicotine patches is less than that for a PBS course of bupropion. Based on the meta-analysis conducted during the evaluation the PBAC considered that nicotine patches are non-inferior to

bupropion. The PBAC also considered that bupropion is more toxic than nicotine patches. The Committee noted that if other costs were also taken into account, including general practitioner consultations for the management of adverse events associated with bupropion, this would favourably affect the cost effectiveness of nicotine patches.

Hence, based on the totality of the evidence, the PBAC considered that the claim of non-inferiority of nicotine patches to varenicline to be uncertain with the evidence suggesting that varenicline is more effective and more toxic, that the evidence supports nicotine patches being more effective and less safe than placebo, and that nicotine patches are of non-inferior efficacy to bupropion and of superior safety.

The PBAC considered that the submission's estimate of the utilisation of nicotine patches is highly uncertain, and substantially underestimated. The PBAC considered that the estimations of substitution of nicotine patches for varenicline were substantially overestimated in the submission, and considered that a number of patients may try more than one type of PBS subsidised smoking cessation therapy. The PBAC noted the sensitivity analysis undertaken by the DUSC indicating the cost implications of variation of the extent of substitution of nicotine patches for varenicline, variation in compliance with 12-weeks therapy and potential 'unmet need' for NRT as a result of people not being able to afford over-the-counter NRT.

Due to the highly uncertain utilisation and consequently highly uncertain overall cost to the Government of the listing of nicotine patches, the PBAC recommended that further advice on the utilisation and overall estimated cost of the listing of nicotine patches be sought by the Department in order to adequately inform the Minister.

In considering the submission, the PBAC also noted the comments received from consumers, health professionals and from a number of organisations in relation to the submission.

The PBAC requested that the Department write to each of the sponsors of nicotine transdermal patches to invite the sponsors to list under this recommendation.

Recommendation:
NICOTINE, transdermal patch, releasing 15 mg per 16 hrs

Add the following indication to the current restriction:

> Authority required:
> 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 initial authority application.

NOTE:
A maximum of 12 weeks of PBS-subsidised nicotine replacement therapy will be authorised per year. No applications for increased maximum quantity and/or repeats will be authorised.

Maximum quantity: 28
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

The Cancer Council Victoria and other consortium members thank the PBAC and Departmental staff for their careful consideration of this submission. We believe that listing of an NRT product on the PBS will increase clinically appropriate use of NRT and improve quit rates in Australian smokers, particularly in people living with mental illness and other disadvantaged groups among whom smoking rates are substantially higher than in the rest of the population.