5.09 NICOTINE, Gum 2 mg, Gum 4 mg, Lozenge 2 mg, Lozenge 4 mg, Nicotinell®, Orion Laboratories Pty Ltd

1 Purpose of Application

1.1 The submission requested that nicotine gum and lozenges be listed on the PBS as a restricted benefit for treating nicotine dependence in cigarette smokers who wish to quit and enter into a behavioural support program.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Cigarette smokers who have indicated they are ready to quit smoking
Intervention	Nicotine gum 2-4 mg Nicotine lozenge 2-4 mg
Comparator	Nicotine patch
Outcomes	Sustained abstinence
Clinical claim	In cigarette smokers, nicotine gum or lozenges are no worse in efficacy in inducing smoking cessation, and no worse in safety, than nicotine patches.

Source: Compiled during the evaluation

2 Requested listing

Suggested additions are in *italics* and deletions are in ~~strikethrough~~.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed price per maximum Qty	Proprietary Name and Manufacturer	
NICOTINE					
Gum 2mg, 216	1	2	$52.64		
Gum 4 mg, 216	1	2	$52.64	Nicotinell®	Orion Laboratories Pty Ltd
Lozenge 2 mg, 216	1	2	$52.64		
Lozenge 4 mg, 216	1	2	$52.64		

Category / Program	GENERAL – General Schedule (Code GE)
Condition:	Nicotine dependence
PBS Indication:	Nicotine dependence
Restriction:	☒Restricted benefit

Clinical criteria:	~~**Clinical criteria 1:**~~ The treatment must be as an aid to achieving abstinence from smoking, AND The treatment must be the sole PBS-subsidised therapy for this condition, AND Patient must have indicated they are ready to cease smoking, AND Patient must have entered a comprehensive support and counselling program, AND Patient must not receive more than 12 weeks of PBS-subsidised nicotine replacement therapy per 12-month period. ~~Details of the support and counselling program must be documented in the patient's medical records at the time treatment is initiated.~~ ~~**Clinical criteria 2:**~~ ~~• The treatment must be the sole PBS-subsidised therapy for this condition,~~ ~~**AND**~~ ~~• Patient must have indicated they are ready to cease smoking,~~ ~~**AND**~~ ~~• Patient must be entering a comprehensive support and counselling program during the consultation at which this prescription is written,~~ ~~**AND**~~ ~~• Patient must not receive more than 12 weeks of PBS-subsidised nicotine replacement therapy per 12-month period.~~ ~~Details of the support and counselling program must be documented in the patient's medical records at the time treatment is initiated.~~ ~~**Clinical criteria 3:**~~ ~~The treatment must be the sole PBS-subsidised therapy for this condition. Only 2 courses of PBS-subsidised nicotine replacement therapy may be prescribed per 12-month period. Benefit is improved if used in conjunction with a comprehensive support and counselling program.~~
~~**Population criteria:**~~	~~**For Clinical criteria 3 only:**~~ ~~Patient must be an Aboriginal or a Torres Strait Islander person.~~
Prescriber Instructions	~~N/P~~atient must be undergoing concurrent counselling for smoking cessation through a comprehensive support and counselling program or is about to enter such a program at the time PBS-subsidised treatment is initiated.
Administrative Advice	~~N/A~~ No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
NICOTINE					
Gum 2mg, 216	1	2	$52.64		
Gum 4 mg, 216	1	2	$52.64	Nicotinell®	Orion Laboratories Pty Ltd
Lozenge 2 mg, 216	1	2	$52.64		
Lozenge 4 mg, 216	1	2	$52.64		

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐ Dental ☒ Medical Practitioners ☒ Nurse practitioners ☐ Optometrists ☐ Midwives
Condition:	Nicotine dependence

PBS Indication:	Nicotine dependence
Restriction Level / Method:	☒Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required - Emergency ☐Authority Required - Electronic ☐Streamlined
Clinical criteria:	The treatment must be the sole PBS-subsidised therapy for this condition.
Population criteria:	Patient must be an Aboriginal or a Torres Strait Islander person
Note:	Only 2 courses of PBS-subsidised nicotine replacement therapy may be prescribed per 12-month period. Benefit is improved if used in conjunction with a comprehensive support and counselling program.
Administrative Advice:	No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised.

2.1 The submission presented a cost-minimisation analysis of nicotine gum and nicotine lozenges compared with nicotine patches.

2.2 The manner of administration, dosing and length of treatment for nicotine gum and lozenges is as follows:

- <u>For nicotine lozenges:</u>
  The proposed dosing schedule in the Product Information (PI) for nicotine lozenges is consistent with that in the trials reported in the submission, and consists of the use of one lozenge every 1-2 hours for the first 6 weeks, followed by one lozenge every 2-4 hours for weeks 7-9, and a lozenge every 4-8 hours for weeks 7-12. Further, the PI recommends a minimum of 9 lozenges for the first 6 weeks, with no more than 15 lozenges per day overall. If recommended for listing, the PBAC is therefore requested to consider whether a separate restriction for nicotine lozenges, including the dose titration schedule, is warranted.

- <u>For nicotine gum:</u>
  The PI for the nicotine gum recommends using a maximum of 20 pieces per day of the 2 mg strength. It also states that highly dependent smokers, or those who failed to quit while using 2 mg strength gum, be prescribed 4 mg strength gum, with a maximum of 10 pieces per day. The PI further recommends a gradual dose titration after 3 months. As such, the PBAC may wish to consider if the maximum quantity of the 2 mg and 4 mg strengths of the gum should be 1680 and 840, respectively (compared to proposed 648, which is derived from the trials included in the submission, where the 4 mg strength was down-titrated in weeks 1-6, 7-9 and 9-12).

2.3 The sponsor's Pre-Sub-Committee-Response (PSCR) (p3) argued that the increase in quantity may result in wastage and could be a safety issue. Further, the PSCR claimed that 648 pieces over 3 months, or 216 pieces per script, offered a reasonable balance by providing adequate treatment for the majority of patients while minimising the wastage. The ESC noted the PSCR's arguments, but considered

that the proposed maximum quantity would result in under-treatment for some patients and may trigger discontinuation in others, and therefore it was likely that the efficacy observed in the trials would not be reached in clinical practice. The pre-PBAC response (p1) expressed the sponsor's willingness to revise the proposed restriction to reflect the current clinical guidelines, the PI and common practice.

2.4 The requested PBS restriction aligns with the current PBS restriction for the sponsor-branded nicotine patches, and the approved Product Information for nicotine gum and lozenges. The ESC noted that the PBS-listed nicotine patches are currently suitable for prescribing by nurse prescribers.

2.5 Patients who begin on nicotine replacement therapy might also switch to treatment with bupropion or varenicline, depending on patient preferences and tolerance. Further, the ESC noted that the gum and lozenges are recommended as better alternatives to nicotine patches for pregnant women and lactating mothers. The ESC also considered that the availability of the sublingual delivery method of nicotine replacement therapy (NRT) on the PBS could be a favourable option in patients with skin conditions, or those who experience skin irritation due to the use of nicotine patches.

For more detail on PBAC's view, see section 7 "PBAC outcome."

3 Background

3.1 TGA status: This brand of nicotine gum was TGA registered on 26 August 2016 as an aid in the cessation of smoking in smokers with nicotine dependence. This brand of nicotine in lozenge form was TGA registered on 23 June 2016 for the relief of nicotine withdrawal symptoms, including cravings associated with smoking cessation.

3.2 Nicotine gum and nicotine lozenges have not been previously considered by the PBAC.

3.3 The Nicotinell® brand of nicotine patches are available through the PBS, while several other brands of nicotine patches ranging in strength from 5-25 mg are available on the PBS, as well as the RPBS. Varenicline and bupropion are the other nicotine dependence treatments currently listed on the PBS.

For more detail on PBAC's view, see section 7 "PBAC outcome."

4 Population and disease

4.1 Cigarette smoking is a known risk factor for numerous cancers, cardiovascular disease and other health issues with significant detriment to patient quality of life. The nicotine found in cigarettes is rapidly absorbed through the skin and respiratory tract, and has stimulatory and addictive effects through acting on the central and

peripheral nervous system. Nicotine gum and lozenges are forms of NRT, and may be used in treating nicotine dependence amongst smokers by providing a safer form of nicotine at doses which are lowered over time.

4.2 Based on guidelines from the Royal Australian College of General Practitioners, smokers may be treated with pharmacotherapy if they are considered nicotine dependent. Nicotine in gum and in lozenge form is intended to offer an additional treatment option to nicotine patches for NRT.

For more detail on PBAC's view, see section 7 "PBAC outcome."

5 Comparator

5.1 The submission nominated nicotine patches as the comparator. The ESC considered that this was reasonable.

For more detail on PBAC's view, see section 7 "PBAC outcome."

6 Consideration of evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

Nicotine lozenges versus nicotine patches

6.3 For the direct comparison between nicotine lozenges with nicotine patches, the submission was based on three head-to-head randomised trials: Schnoll (2010) (N = 642), Piper (2009) (N = 1,504) and Smith (2009) (N = 1,346).

6.4 Details of the trials presented in the submission for the direct comparison are provided in the table below.

Table 2: Trials and associated reports presented in the submission

Trial ID/First Author	Protocol title/ Publication title	Publication citation
Direct randomised trials (comparison of lozenge versus patch)		
Piper 2009	Piper, ME, et al. "A Randomized Placebo-Controlled Clinical Trial of 5 Smoking Cessation Pharmacotherapies."	Archives of general psychiatry 2009; 66(11):1253-62.
Schnoll 2010	Schnoll, RA., et al. "Nicotine Patch Vs. Nicotine Lozenge for Smoking Cessation: An Effectiveness Trial Coordinated by the Community Clinical Oncology Program."	Drug & Alcohol Dependence 2009;107(2-3):237-43

Trial ID/First Author	Protocol title/ Publication title	Publication citation
Smith 2009	Smith, SS, et al. "Comparative Effectiveness of 5 Smoking Cessation Pharmacotherapies in Primary Care Clinics."	Archives of internal medicine 2009; 169(22): 2148-55

Source: Tables B-6, p42 and B-15, p59-60 of the submission.
[a] Updated to include 11 studies on patch versus control

6.5 The key features of the randomised trials used in the direct comparison between nicotine lozenges and nicotine patches are summarised in the table below.

Table 3: Key features of the included evidence, direct comparison of nicotine lozenges versus patches

Trial	N	Design/ duration of follow-up	Risk of bias	Patient population	Outcome	Use in CMA
Piper (2009)	1,504	R, DB 6 mths	Low	Adults smoking ≥ 10 cigarettes per day	Sustained abstinence rate	Utilisation of lozenges
Schnoll (2010)	642	R, OL 6 mths	Low			Not used
Smith (2009)	1,346	R, OL 6 mths	High			Not used

Source: compiled during the evaluation
CMA = cost minimisation analysis DB = double blinded; OL= open label; R = randomised.

6.6 Piper (2009), Smith (2009) and Schnoll (2010) were used by the submission to inform the efficacy and safety of nicotine lozenges compared with nicotine patches. Piper (2009) was also used to inform the cost-minimisation analysis for the nicotine lozenge. The population in Piper (2009) might not represent the target PBS population, as the participants underwent intensive screening and would have had to be highly motivated to be included in the study. Also, participants in Piper (2009) had five treatment visits during the first 12 week period, which might be greater than required in the Australian setting.

6.7 The submission used sustained abstinence as the primary efficacy outcome for the trials comparing nicotine lozenges to nicotine patches, and nicotine gum to nicotine patches. Sustained abstinence was defined as:

- continuous abstinence since quitting;
- self-reported abstinence for a prolonged period; or,
- repeated point prevalence abstinence (with or without biochemical validation) at multiple follow-ups
    - Point prevalence abstinence is measured at a single point in follow-up, and is often confirmed by biochemical tests such as exhaled carbon monoxide or saliva cotinine tests.

<u>Nicotine gum versus nicotine patches</u>

6.8 The submission conducted an indirect comparison between nicotine gum and nicotine patches. This was reasonable, as the single direct randomised trial of nicotine gum versus patches (Moolchan, 2005) identified by the submission provided inadequate evidence for the relative efficacy and safety of nicotine gum to patches.

6.9 For the indirect comparison between nicotine gum with nicotine patches, the submission was based on a meta-analysis conducted using a Cochrane review of nicotine replacement therapies (Stead, 2012) updated with an additional 11 studies comparing nicotine patches with control. Approximately 52,000 patients were considered in the meta-analysis. Details of the trials used in the indirect comparison between nicotine gum with nicotine patches is presented in the table below.

Table 4: Trials and associated reports presented in the submission

Trial ID/First Author	Protocol title/ Publication title	Publication citation
Systematic review (indirect comparison of gum versus patch)		
Stead 2012[a]	Stead, Lindsay F, et al. "Nicotine Replacement Therapy for Smoking Cessation."	Cochrane Database of Systematic Reviews 2012; 11.
Additional randomised trials added to Stead for meta-analysis of indirect comparison of gum versus patch		
Antheneli 2016	Anthenelli, R. M., 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.
Berlin 2014	Berlin, I., et al. "Nicotine Patch in Pregnant Smokers: Randomised, Placebo Controlled, Multicentre Trial of Efficacy."	BMJ 2014; 348: g1622.
Bullen 2013	Bullen, C., et al. "Electronic Cigarettes for Smoking Cessation: A Randomised Controlled Trial."	Lancet 2013; 382 (9905): 1629-37.
Cummins 2016	Cummins, S. E., et al. "Helping Hospitalized Smokers: A Factorial Rct of Nicotine Patch and Counseling."	American Journal of Preventive Medicine 2016; 51(4): 578-86.
Cunningham 2016	Cunningham, J. A., et al. "Effect of Mailing Nicotine Patch on Tobacco Cessation among Adult Smokers: A Randomized Clinical Trial."	JAMA Internal Medicine 2016; 176(2): 184-90.
El-Mohandes 2013	El-Mohandes, A. A., et al. "A Randomized Clinical Trial of Trans-Dermal Nicotine Replacement in Pregnant African-American Smokers."	Maternal & Child Health Journal 2013; 17(5): 897-906.
Heydari 2012	Heydari, G, et al. "Quitting Smoking with Varenicline: Parallel, Randomised Efficacy Trial in Iran."	The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2012;16(2): 268-72.
Lee 2015	Lee, S. M., et al. "Long-Term Quit Rates after a Perioperative Smoking Cessation Randomized Controlled Trial."	Anesthesia & Analgesia 2015; 120(3): 582-7.
Scherphof 2014	Scherphof, C. S., et al. "Long-Term Efficacy of Nicotine Replacement Therapy for Smoking Cessation in Adolescents: A Randomized Controlled Trial".	Drug & Alcohol Dependence 2014; 1402: 17-20.
Tuisku 2016	Tuisku, A., et al. "Varenicline and Nicotine Patch Therapies in Young Adults Motivated to Quit Smoking: A Randomized, Placebo-Controlled, Prospective Study."	Basic & Clinical Pharmacology & Toxicology 2016; 119(1): 78-84.
Ward 2013	Ward, K. D., et al. "Randomized Trial of the Effectiveness of Combined Behavioural/Pharmacological Smoking Cessation Treatment in Syrian Primary Care Clinics."	Addiction 2013; 108(2): 394-403.

Source: Table B-15, p59-60 of the submission.

[a] Updated to include 11 studies on patch versus control

6.10 Table 5 summarises the key features of the included evidence in the indirect comparison between nicotine gum and nicotine patches.

Table 5: Key features of the included evidence – indirect comparison of nicotine gum versus patches

Trial	N	Design/ duration of follow-up	Risk of bias	Patient population	Outcome(s)	Use in CMA
Nicotine gum versus control						
Stead 2012[a] (161 trials)	24,534	56 out of 161 trials in the update to Stead (2012) compared nicotine gum with control.				Utilisation of gum
Nicotine patch versus control						
Stead 2012[a] (161 trials)	28,059	54 out of 161 trials in the update to Stead (2012) review compared nicotine patches with control.				Not used

Source: compiled during the evaluation
CMA = cost-minimisation analysis
[a] Updated to include 11 patch versus control trials

6.11 The trials presented by the submission for the indirect comparison between nicotine gum with nicotine patches were broadly consistent with the requested PBS listing in terms of the interventions provided and the patient population. Whilst there was considerable heterogeneity between the trials, it is unlikely that the estimated efficacy and safety of nicotine gum relative to nicotine patches would be affected given the considerable number of participants included.

6.12 The submission used sustained abstinence as the primary efficacy outcome for the trials comparing nicotine gum to nicotine patches. The same definition of sustained abstinence was used as in the comparison between nicotine lozenges and nicotine patches.

Comparative effectiveness

Nicotine lozenges versus nicotine patches

6.13 Table 6 summarises six-month smoking abstinence rates across the direct randomised trials, and the meta-analysis conducted by the submission.

Table 6: Results of smoking cessation across the direct randomised trials

Trial ID	Nicotine lozenge n/N (%)	Nicotine patches n/N (%)	RD (95% CI)	RR (95% CI)	P-value
Piper (2009)[a]	87/260 (33.5%)	90/262 (34.4%)	-0.01 (-0.09, 0.07)	0.97 (0.77, 1.24)	0.830
Schnoll (2010)	35/321 (10.9%)	50/321 (15.6%)	-0.05 (-0.1, 0.01)	0.70 (0.47, 1.05)	0.083
Smith (2009)	53/261 (20.3%)[b]	50/282 (17.7%)	0.03 (-0.04, 0.09)	1.15 (0.81, 1.62)	0.445
Meta-analysis	**Nicotine lozenge n/N (%)**	**Nicotine patches n/N (%)**	**RD (95% CI)**	**RR (95% CI)**	
Random effects model[c]	175/842 (20.8%)	190/865 (22%)	-0.014 (-0.059, 0.031)	0.94 (0.74, 1.18)	
Chi-square for heterogeneity			0.236	0.187	
I^2 statistic			30.71	40.35	

Source: Tables B-28, p83-84 and B-51, p96 of the submission and calculated during the evaluation.
CI = confidence interval; RD = risk difference; RR = relative risk
[a] Number of people with smoking abstinence at 6 months cannot be verified from the publications as only percentages were provided
[b] smoking abstinence in Smith (2009) was 19.9%.
[c] Random effects meta-analysis, adjusted to include abstinence of 19.9% (n = 52) for the lozenge arm of Smith (2009).

6.14 The three head-to-head trials, and a meta-analysis conducted by the submission, comparing nicotine lozenges with nicotine patches showed no significant differences between the two treatments. The meta-analysis of the three head-to-head trials was consistent with the published results for each individual study, and the analysis

conducted by Stead (2012) comparing nicotine lozenges with patches (RR = 0.94, 95% CI: 0.79 to 1.12, p = 0.54).

6.15 In the Smith (2009) trial, the 6 month abstinence rate was 19.9% and not 20.3% as stated in the submission; however, this had limited effect on the overall result of the meta-analysis.

6.16 The submission did not specify a non-inferiority margin. The 95% confidence interval indicated the efficacy of nicotine lozenges (RR = 0.94, 95% CI: 0.74 to 1.18) could be 26% lower than that for the patches. The ESC considered that the submission's claim of non-inferiority was likely to be reasonable, as the point estimate was close to 1, and the 95% CI spanned reasonably equally above and below unity. The ESC also noted that the Piper (2009) study concluded that combination therapy using both nicotine patches and lozenges was the most effective treatment arm.

6.17 The submission presented data on patient adherence to nicotine lozenges and patches. An adherence rate of 67% based on Piper (2009) was applied to the recommended dose in the PI for nicotine lozenges. Briefly, the submission estimated that, in a 12-week period, individuals would consume 10 lozenges/day for weeks 1-6, 7 lozenges/day for weeks 7-9 and 3 lozenges/day for weeks 10-12. The submission assumed a 100% compliance rate for the patches, and that patients would use 84 patches over a 12-week treatment period.

6.18 Data informing patient adherence was used by the submission in the estimation of the equi-effective doses for nicotine lozenges and gum in the cost-minimisation analysis, and is discussed in further detail (see 6.38 and 6.48 below). It was noted during the evaluation that there is considerable uncertainty and variation in the number of lozenges administered across the trials.

<u>Nicotine gum versus nicotine patches</u>

6.19 Table 7 presents the results of the indirect comparison of abstinence rates between nicotine gum and patches.

Table 7: Indirect comparison of abstinence rates between nicotine gum versus nicotine patches

	Trials of nicotine gum			Trials of nicotine patches			Indirect estimate of abstinence Indirect RR (95% CI)
	Abstinence RR (95% CI)	**Gum n/N (%) N = 10,596**	**Placebo n/N (%) N =11,986**	**Placebo n/N (%) N = 11,912**	**Patch n/N (%) N = 16,073**	**Abstinence RR (95% CI)**	
Stead (2012) updated meta analysis[a]	**1.49 (1.36, 1.64)**	1,732 (16.3%)	1,196 (10.0%)	1,072 (9.0%)	2,391 (14.9%)	**1.63 (1.49, 1.79)**	0.91 (0.80, 1.04)

Source: Tables B-52 to B-55, pp97-101 of the submission and calculated during the evaluation
CI = confidence interval; n = number with event; N = number in group; RR = relative risk
[a] pooled using the random effects model
Bold = statistically significant

6.20 Based on the results of the indirect comparison, the submission concluded that no statistically significant differences were observed between nicotine gum and nicotine patches in efficacy.

6.21 During the evaluation, a random effects meta-analysis was conducted and a moderate degree of heterogeneity was identified. However, despite heterogeneity, the analyses presented by the submission were considered reasonable and aligned with existing reviews on smoking cessation therapy (Stead (2012) and Cahill (2013)).

6.22 The submission did not specify a non-inferiority margin. The 95% confidence interval indicated the efficacy of nicotine gum (RR: 0.91; 95% CI: 0.80 to 1.04) could be 20% lower than that for the patches. The ESC considered that the submission's claim of non-inferiority was not adequately supported by the evidence presented in the submission, particularly given that the upper limit of the 95% CI only just crosses unity.

6.23 The submission presented data on patient adherence to nicotine gum and patches. The mean number of pieces of gum used per day in Garvey (2000), Harackiewicz (1988) and Jarvis (1982) was used to estimate patient adherence to nicotine gum. The ESC noted that the submission did not provide a rationale for presenting data from these three specific trials, over others. Briefly, the submission estimated that, in a 12-week period, individuals would initially consume approximately 7 pieces/day of nicotine gum, decreasing to 4-5 pieces/day until week 12. The submission assumed a 100% compliance rate for the patches, and that patients would use 84 patches over a 12-week treatment period.

6.24 Data informing patient adherence was used by the submission in the estimation of the equi-effective dose for nicotine gum in the cost-minimisation analysis (see 6.42 below). It was noted during the evaluation that there is considerable uncertainty and variation in the number of pieces gum administered across each trial.

Comparative harms

6.25 The key safety concerns for nicotine lozenges compared with patches included nausea or vomiting, oral reactions and hiccups. Key safety concerns for nicotine gum compared with patches included hiccups and oral reactions; after excluding Moolchan (2005) from the indirect safety comparison, patients using nicotine gum were at a greater risk of oral reaction.

6.26 The exclusion of Moolchan (2005) in the sensitivity analysis of the indirect comparison was reasonable, as participants in the trial were randomised to receive either nicotine gum or patches rather than control. The safety comparisons performed by the submission aligned with the current Product Information for nicotine gum and nicotine lozenges.

Benefits and harms

Nicotine lozenges versus patches

6.27 A summary of the comparative benefits and harms for nicotine lozenges versus patches is presented in the table below.

Table 8: Summary of comparative benefits and harms for nicotine lozenges and nicotine patches

Benefits						
Sustained abstinence						
Trial	**Nicotine lozenge[b] n/N (%)**	**Nicotine patch[b] n/N(%)**	**RR (95% CI)**	**Events/100 patients[a]**		**RD (95% CI)**
				Nicotine lozenge	**Nicotine Patch**	
Meta-analysis						
Random-effects model[c]	175/842 (20.8%)	190/865 (22%)	0.94 (0.74, 1.18)	21	22	-0.014 (-0.059, 0.031)
Chi-square for heterogeneity			0.187	-	-	0.236
I^2 statistic			40.35	-	-	30.71
Harms						
Trial	**Nicotine lozenge n/N (%)**	**Nicotine patch n/N(%)**	**OR (95% CI)**	**Events/100 patients[a]**		**RD (95% CI)**
				Nicotine lozenge	**Nicotine patch**	
Nausea/vomiting						
Piper (2009)	44/260 (16.9%)	25/262 (25.2%)	**1.93 (1.14, 3.26)**	17	9	**0.07 (0.02, 0.13)**
Sleep problems						
Piper (2009)	18/260 (6.9%)	66/262 (25.2%)	**0.22 (0.13, 0.38)**	7	25	**-0.18 (-0.24, -0.12)**
Skin reaction						
Piper (2009)	3/260 (1.1%)	86/262 (32.8%)	**0.02 (0.01, 0.08)**	1	33	**-0.32 (-0.38, -0.26)**
Oral reaction						
Piper (2009)	38/260 (14.6%)	11/262 (4.2%)	**3.91 (1.95, 7.83)**	15	4	**0.10 (0.06, 0.15)**
Hiccups						
Piper (2009)	35/260 (13.5%)	0/262 (0.0%)	**82.65 (5.04, 1355.04)[a]**	13	0	**0.13 (0.09, 0.18)**

Source: compiled during the evaluation and calculated during the evaluation
CI = confidence interval OR = odds ratio; RD = risk difference; RR = relative risk
[a] Maximum duration of follow-up: Piper (2009) = 6 months; Scnholl (2010)= 6 months; Smith (2009) = 6 months
[b] Number of people with smoking abstinence at 6 months cannot be verified from the publications as only percentages were provided
[c] smoking abstinence in Smith (2009) was 19.9%

6.28 On the basis of the direct evidence presented by the submission, for every 100 patients treated with nicotine lozenges in comparison to nicotine patches over a maximum duration of treatment of 12 weeks:

- There was no difference in the proportion of individuals achieving sustained abstinence;
- Approximately eight more patients would experience nausea or vomiting;
- Approximately ten more patients would experience an oral reaction; and
- Approximately 13 more patients would experience hiccups.
- Approximately 32 fewer patients would experience a skin reaction.
- Approximately 18 fewer patients would experience sleep problems.

Nicotine gum versus patches

6.29 A summary of the comparative benefits and harms between nicotine gum and nicotine patches is presented below.

Table 9: Summary of comparative benefits and harms for nicotine gum and nicotine patches (indirect comparison)

Benefits						
Stead 2012 (Nicotine gum versus control trials (N=56)) Random effects meta-analysis						
Sustained abstinence	**Nicotine gum n/N (%) (N = 10,596)**	**Placebo n/N (%) (N = 11,986)**	**RR (95% CI)**	**Event rate/100 patients[a]**		**RD (95% CI)**
				Nicotine gum	**Placebo**	
	1732 (16.3%)	1196 (10.0%)	1.49 (1.36, 1.64)	16	10	0.05 (0.04, 0.07)
Chi-square for heterogeneity			0.002	-	-	<0.001
I^2 statistic with 95% uncertainty interval			39.2	-	-	60.4
Stead 2012[b] (Nicotine patch versus control trials (N=54)) Random effects meta-analysis						
Sustained abstinence	**Nicotine patch n/N (%) (N = 16,073)**	**Placebo n/N (%) (N = 11,912)**	**RR (95% CI)**	**Event rate/100 patients[a]**		**RD (95% CI)**
				Nicotine patch	**Placebo**	
	2,391 (14.9%)	1,072 (9.0%)	1.63 (1.49, 1.79)	15	9	0.061 (0.048, 0.074)
Chi-square for heterogeneity			0.068	-	-	<0.001
I^2 statistic with 95% uncertainty interval			23.28	-	-	60.73
Indirect comparison: Stead (2012) Gum versus Patch trials			0.91 (0.80, 1.04)	-		-0.01 (-0.028, 0.01)
Harms: Random-effects meta-analysis						
	Nicotine Gum	**Nicotine Patch**	**OR (95% CI)**	**Events /100 patients**		**RD (95% CI)**
				Nicotine Gum	**Nicotine Patch**	
Indirect comparison of Gum versus Patch trials						
Hiccups			**10.54 (2.70, 41.09)** 18.16 (0.70, 467.66)[c]	NA		NA
Oral reactions			**3.19 (1.28, 7.93)** **3.15 (1.19, 8.35)[c]**	NA		NA

Source: Compiled and calculated during the evaluation
CI = confidence interval; NA = not assessed; OR = odds ratio; RD = risk difference; RR = relative risk
Bold = significant
[a] The duration of follow-up was at least 12 months for 64% of gum versus control trials, and 54% of patch versus control trials.
[b] Based on 43 patch versus control trials in Stead (2012) and an additional 11 patch versus control trials identified by the submission
[c] Results are based on a sensitivity analysis with Moolchan (2005) removed.

6.30 On the basis of the indirect evidence presented by the submission, the comparison between nicotine gum and nicotine patches demonstrated that nicotine gum resulted in:

- No significant differences in the likelihood of achieving 6-month abstinence
- A 10-fold increase in the odds of experiencing hiccups.
- A three-fold increase in the odds of experiencing an oral reaction.

Clinical claim

6.31 The submission described nicotine gum and nicotine lozenges as non-inferior in terms of comparative efficacy and safety compared with nicotine patches. This was adequately supported for statistical non-inferior efficacy and safety, as:

- A similar level of efficacy in achieving sustained abstinence was observed in the three trials comparing nicotine lozenges with nicotine patches and in the indirect comparison between nicotine gum and nicotine patches despite moderate heterogeneity between trials.
  - This was consistent with the conclusions of similar analyses conducted in a Cochrane review of NRT (Stead, 2012).

  - Although the difference in abstinence rates was not statistically significant between nicotine gum or lozenges when compared with patches, it was noted during the evaluation that there was the potential for a lower level of efficacy with the gum and lozenges compared with the patches (20% for nicotine gum and 26% for nicotine lozenges).
- Adverse events experienced by participants receiving nicotine gum or lozenges were similar to those experienced by participants receiving nicotine patches, with hiccups and oral reactions occurring more frequently amongst participants using nicotine gum or lozenges. This was consistent with the PI for both nicotine gum and lozenges.
- The PSCR (p1) claimed that all three forms of NRT would have similar efficacy in a real life setting given the evidence from clinical trials and meta-analysis, but did not provide any evidence to justify this claim.
- The ESC considered that while the submission's claim of non-inferiority to nicotine patches was likely to be reasonable for the nicotine lozenges (RR = 0.94, 95% CI: 0.74 to 1.18), the evidence presented for the nicotine gum (RR: 0.91; 95% CI: 0.80 to 1.04) was unlikely to be sufficient for a non-inferiority claim, particularly given that the upper limit of the 95% CI only just crosses unity.

6.32 The pre-PBAC response re-iterated the submission's claim of non-inferiority, citing the Cochrane overview of smoking cessation (Cahill et al. 2013), which concluded that there was little difference between the gum, patch, or lozenge forms of NRT.

6.33 The PBAC noted ESC's uncertainty regarding the non-inferior efficacy claim for nicotine gum versus nicotine lozenges, however considered that on balance, the submission's overall claim of non-inferiority in terms of comparative efficacy and safety for nicotine gum and lozenges compared with nicotine patches, was reasonable.

Economic analysis

Nicotine lozenges

6.34 The submission presented a cost-minimisation analysis of nicotine lozenges versus nicotine patches. This was in line with the clinical evidence of non-inferior efficacy and safety of nicotine lozenges compared with patches.

6.35 Table 10 summarises the estimated mean number of nicotine lozenges consumed over a 12-week treatment period, and the estimated equi-equivalent dose.

Table 10: Estimated number of nicotine lozenges required for a 12-week course of treatment

Time Period	Mean Number of lozenges per Day	Number of Days in Period	Mean Number of lozenges per period[a]	Mean Number of patches per period[b]
Weeks 1-6	10	42	420	36.12
Weeks 7-9	7	21	147	18.06
Weeks 9-12	3	21	63	18.06
Total	**-**	**84**	**630**	**72.24**

Source: Table D-2, p112 of the submission and calculated during the evaluation

[a] Based on an adherence of 67% from the Piper (2009) trial
[b] Based on an adherence of 86% from the Piper (2009) trial

6.36 The submission estimated the equi-effective doses as:

- 630 nicotine lozenges, was equivalent to 84 nicotine patches in a 12-week treatment period (1 patch = 7.5 lozenges).

6.37 The submission estimated the mean number of lozenges consumed per day, and the number of patches used over a 12-week period, based on:

- An adherence rate of 67% to nicotine lozenges based on Piper (2009) applied to the recommended dosage for nicotine lozenges described in the PI; and
- The assumption that all patients would use one nicotine patch per day over 12 weeks.

6.38 There was considerable uncertainty in the estimation of the equi-effective doses for lozenges, as:

- The submission did not assess the impact of differences between the maximum dose allowed for the 2 mg and 4 mg nicotine lozenge on the equi-effective dose, as patients were assigned to either 2 mg or 4 mg arms in the Piper (2009) trial, and no changes between strengths occurred.
- Applying a 67% adherence rate from Piper (2009) to the recommended dose of nicotine lozenges in the PI was uncertain.
    - It was not stated in the PI what trial was used and there may be variation on what was considered 100% adherence in the trial and what the submission considered was 100% adherence.
    - The submission assumed that 67% adherence was 630 lozenges over 12 weeks, based on the Nicotinell Lozenge® PI. This would imply that 100% compliance was 940 lozenges. This may have been an underestimate as the maximum number of lozenges a patient can receive was 1,260 lozenges over the 12 week period based on the Nicotinell Lozenge® PI (15 per day).
    - Adherence rate of nicotine lozenges in a clinical setting could be different than that reported in the Piper (2009) trial, as trial participants underwent intensive screening and would have had to be highly motivated to quit to be included. Furthermore, participants in Piper (2009) had five visits during the first 12 week period, which might be greater than required in the Australian setting.
    - The submission provided supplementary data from other trials in support of data from Piper (2009). However, it was not possible to use these trials to determine an equi-effective dose of lozenge versus patch, as none of the supportive trials included a nicotine patch treatment arm; rather, nicotine lozenges were compared with either a placebo arm or a behavioural support program.

6.39 Furthermore, the assumption that patients would use 84 nicotine patches over 12 weeks of treatment in the determination of the equi-effective dose lozenges was inappropriate, as:

- The submission did not present clinical adherence data for nicotine patches from the Piper (2009) trial. During the evaluation, it was noted that 86% of patients were adherent to patches in the trial. Based on this, it was estimated that patients would require 72 patches over 12 weeks. However, the assumption of an 86% adherence rate to patches based on the Piper (2009) trial is also associated with uncertainty due to the differences between the trial and proposed PBS populations.
- The PSCR (p3) claimed that it was unlikely that the dose relativity proposed in the evaluation would be reflected in real world usage of the nicotine gum and lozenges, noting that the Piper (2009) study was conducted in a highly enriched population with intensive psychological support before and after randomization, and therefore this study had very low discontinuation rates (<10%). The PSCR (p3) further stated that the ability to self-titrate the dose of gum and lozenges was separate to non-compliance/discontinuation, and that the patches deliver a fixed daily dose and must be used daily to be effective.
- The ESC noted that the Piper (2009) was used by the submission to estimate lozenge usage (lozenge compliance) in the determination of the equi-effective dose, but considered that the submission's assumption of 100% usage of nicotine patches rather than the actual compliance to patches reported in the trial, was inappropriate. The ESC considered that while the Piper (2009) study has its limitations, it provided the best direct comparison evidence on compliance.

6.40 Ultimately, the ESC agreed that the equi-effective dose for lozenges was uncertain given uncertainty around patient adherence to nicotine lozenges and patches, and variability in the maximum allowed daily dosage of nicotine lozenges between different lozenge strengths.

6.41 Table 11 presents the proposed ex-manufacturer prices of the nicotine patch and lozenge.

Table 11: Ex-manufacturer prices of the nicotine patch and lozenge

	Nicotine Patch	Nicotine Lozenge
Equi-effective dose	28 patches	216 lozenges
Ex-manufacturer for 3 packs (12 weeks)	$117.42	$117.42
Ex-manufacturer/pack	$39.14 -	$39.14 $34.62
DPMQ/pack	$52.64 -	$52.64 $46.60

Source: Table D-8, p118 of the submission and calculated during the evaluation based on adjusted equi-effective dose
DPMQ = dispensed price for maximum quantity

6.42 The submission requested that 2 mg and 4 mg nicotine lozenges have the same ex-manufacturer price, contending that this would ensure adequate treatment for patients. The ESC noted the PSCR's (p4) comments arguing that the approach taken in the submission was appropriate as both the nicotine patches (on the PBS) and lozenges (in the OTC market) have a flat pricing structure, but considered that the prices calculated for nicotine lozenges should take into account the likely use of each of the strengths.

6.43 The adjusted price is also presented in Table 11 above; this was based on the assumption that patient adherence to nicotine patches was 86%, as estimated by the Piper (2009) trial. During the evaluation, it was found that the assumptions used by the submission in the estimation of the equi-effective dose of nicotine lozenges are likely to have resulted in the overestimation of the ex-manufacturer price per pack and DPMQ.

Nicotine gum

6.44 The submission presented a cost-minimisation analysis of nicotine gum versus nicotine patches. This was in line with the clinical evidence of non-inferior efficacy and safety of nicotine gum compared with patches.

6.45 Table 12 summarises the estimated mean number of pieces of gum over a 12-week treatment period, and the estimated equi-effective dose.

Table 12: Estimated number of pieces of nicotine gum required for a 12-week course of treatment

Time Period	Mean Number of pieces per Day	Number of Days in Period	Mean Number of pieces per period[a]	Mean Number of patches per period[b]
Weeks 1-4	9	28	252	24.08
Weeks 5-8	7	28	196	
Weeks 9-12	6	28	168	
Total	**-**	**84**	**616**	**72.24**

Source: Table D-7, p117 of the submission and calculated during the evaluation
[a] Based on adherence from Garvey (2000), Harackiewics (1988) and Jarvis (1982)
[b] Based on an adherence of 86% from the Piper (2009) trial

6.46 The submission estimated the equi-effective dose as: 616 pieces of nicotine gum was equivalent to 84 nicotine patches in a 12-week treatment period (1 patch = 7.3 pieces of gum).

6.47 The submission estimated the mean number pieces of gum consumed per day, and the number of patches used over a 12-week period, based on:

- Mean gum use from Garvey (2000), Harackiewics (1988) and Jarvis (1982); and
- The assumption that all patients would use one nicotine patch per day over 12 weeks.

6.48 There was considerable uncertainty in the estimation of the equi-effective doses for nicotine gum, as:

- The estimate of the equi-effective dose of nicotine gum might have been inappropriate given the considerable heterogeneity between the trials included in the estimate.
- The ESC noted that the submission did not provide a rationale to justify why the Garvey (2000), Harackiewics (1988) and Jarvis (1982) studies were specifically chosen to estimate the appropriate dosage of the nicotine gum. The pre-PBAC response (p2) stated that the three trials were chosen as they provided usage estimates at multiple time points in a consistent manner. The pre-PBAC response (p2) further noted that when all available trials were used, the

estimated number of pieces was considerable lower (about 446 pieces);

- The ESC noted that submission did not assess the impact of differences between the maximum dose allowed for the 2 mg and 4 mg nicotine gum on the equi-effective dose, as patients were assigned to either 2 mg or 4 mg arms in the trials, and no strength switching occurred in the trials.
- During the evaluation, it was noted that 86% of patients were adherent to patches in the trial. Based on this, it was estimated that patients would require 72 patches over 12 weeks during the evaluation. The ESC considered that the assumption that patients would use 84 nicotine patches over 12 weeks of treatment in the determination of the equi-effective dose of nicotine gum and lozenges was inappropriate (see 6.36 above), as it assumed 100% adherence which is unlikely to occur in clinical practice.

6.49 Table 13 presents the proposed ex-manufacturer prices of the nicotine patch and gum.

Table 13: Ex-manufacturer prices of the nicotine patch, lozenge and gum

	Nicotine Patch	Nicotine Gum
Equi-effective dose	28 patches	216 gum pieces
Ex-manufacturer for 3 packs (12 weeks)	$117.42	$117.42
Ex-manufacturer/pack	$39.14 -	$39.14 $35.41
DPMQ/pack	$52.64 -	$52.64 $47.77

Source: Table D-8, p118 of the submission and calculated during the evaluation based on adjusted equi-effective dose
DPMQ = dispensed price for maximum quantity

6.50 The submission requested that 2 mg and 4 mg nicotine gum have the same ex-manufacturer price, contending that this would ensure adequate treatment for patients. The submission did not adequately support this claim, as:

- The maximum allowable daily dose, and therefore the equi-effective dose, was different for 4 mg compared with 2 mg gum.
- The PSCR (p4) acknowledged the uncertainty around the equi-effective dose, but argued that the same ex-manufacturer's price for the 2 mg and the 4 mg gum was proposed in the submission to allow switching between strengths as required, and that it was consistent with the current flat pricing structure of nicotine patches in the OTC market. The ESC considered the prices calculated for the nicotine gum should take into account the likely use of each of the strengths.
- The ESC noted the PSCR (p4) indicated that the sponsor was willing to work with the PBAC on issues relating to the appropriate equi-effective dose and the resultant price.

6.51 The adjusted price is also presented in Table 14 above; this was based on the assumption that patient adherence to nicotine patches was 86%, as estimated by the Piper (2009) trial.

6.52 The ESC considered that the assumptions used by the submission in the estimation of the equi-effective dose of nicotine gum are likely to have resulted in the overestimation of the ex-manufacturer price per pack and DPMQ.

6.53 The submission noted that no differences in other PBS or MBS items were expected compared with those currently incurred whilst treating patients with nicotine patches. This was on the basis of:

- the claim of non-inferior efficacy and safety of nicotine gum/lozenges to patches; and
- the identical restriction proposed for nicotine gum to nicotine patches.

The ESC considered that while these assumptions were likely to be reasonable, nicotine lozenges and gum may be used in combination therapy with nicotine patches, given that the efficacy of nicotine lozenges and gum significantly improved when used in combination with nicotine patches (Piper, 2009). The ESC further considered that although no evidence was provided in the submission about the cost-effectiveness of the combination treatment, it was highly likely that combination use would occur in practice, and would therefore have substantial financial implications.

Drug cost/patient/12 week course: $158

6.54 The submission estimated a drug cost per patient per course of $158 for nicotine lozenges and for nicotine gum. This was based on a dispensed price for maximum quantity (DPMQ) of $53 per 216-piece pack of nicotine lozenges or gum, with three packs expected to provide a full 12-week treatment course.

6.55 During the evaluation, a DPMQ of $47 per pack of nicotine lozenges, and $48 per pack of nicotine gum was estimated based on an assumed trial-based patient adherence rate of 86% for the nicotine patches (Piper, 2009), rather than full compliance as assumed by the submission. Based on a 12-week treatment course using three packs, it is estimated that a full course of nicotine lozenge therapy would cost $140 and a full course of nicotine gum would cost $143. The ESC noted that the price of using the nicotine patches for the 12-week period was $137, using a DPMQ of $53 per pack of the sponsor's brand of the nicotine patches currently listed on the PBS, and based on an assumed trial-based patient adherence rate of 86% (Piper, 2009).

Estimated PBS usage & financial implications

6.56 The submission used a non-standard market share approach based on a combination of the potential shift from the over-the-counter (OTC) lozenge and gum markets and from the existing PBS listed therapies (nicotine patches, varenicline and bupropion) to the potential PBS listed gum and lozenges.

Table 14: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Nicotine gum and lozenges					
Estimated number of people treated with Nicotinell® gum and lozenges					
Gum	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lozenge	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated number of PBS prescriptions for Nicotinell® gum and lozenges					
Nicotine Gum	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nicotine Lozenge	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications of Nicotinell® gum and lozenges					
Cost to PBS/RPBS (2 mg)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Cost to PBS/RPBS (4 mg)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Total cost to PBS/RPBS	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**
Varenicline, nicotine patches and bupropion					
Estimated change in number of people treated					
Varenicline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nicotine patch	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bupropion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated change in PBS prescriptions					
Varenicline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nicotine patch	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bupropion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications for varenicline, nicotine patches and bupropion					
Varenicline cost to PBS/RPBS	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Nicotine patch cost to PBS/RPBS	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Bupropion cost to PBS/RPBS	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Total cost to PBS/RPBS	**-$[redacted]**	**-$[redacted]**	**-$[redacted]**	**-$[redacted]**	**-$[redacted]**
Net financial implications					
Net cost to PBS/RPBS	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**

Source: Commentary p23
PBS = pharmaceutical benefits scheme; RPBS = repatriation pharmaceutical benefits scheme

The redacted table shows that at year 5, the estimated number of PBS prescriptions for Nicotinell® gum and lozenges was 100,000 – 200,000 and the net cost to the PBS would be less than $10 million.

6.57 Sales estimates for OTC NRT were derived from two Intercontinental Marketing Services (IMS) studies of the OTC market for NRT from 2012 to 2016. This was used to predict the OTC market for NRT over the next five years.

6.58 The DUSC considered that it was likely that concomitant use of NRTs were already occurring in practice, noting that the latest clinical guidelines[1] encourage health professionals to consider recommending the use of combination NRT. The DUSC considered that the 2 mg dose of lozenges or gum is likely to be used concomitantly with other therapies in practice, as it provides a short-term boost in nicotine levels. The DUSC considered that the 2 mg dose is unlikely to be effective for heavy smokers and presents a higher risk of concomitant use, which is beyond the requested restriction, compared with the 4 mg strength. The DUSC also noted that switching from one form of NRT to another can be a quitting strategy, but that this was not considered by the submission (switching between lozenges and gum). For these reasons, the DUSC considered the proposed place in therapy for the gum and lozenges may not be appropriate.

6.59 Overall, the DUSC considered that the financial estimates were likely to be underestimated with a high degree of uncertainty, as:

- The submission did not consider the potential additional population who would start lozenges or gum after PBS listing who would not otherwise have attempted smoking cessation therapy. There may be a clinical need for these forms of NRT on the PBS particularly for high risk groups such as those with mental health issues or who have contraindications to the PBS listed therapies or with financial barriers to accessing them OTC. Therefore the eligible population is likely underestimated;
- The methodology used to estimate the extent of cost shifting from the OTC market to the potential PBS market was problematic and would have an unclear impact on the financial estimates;
- The submission assumed no change in the size of the PBS listed smoking cessation therapy market over the five year estimates, which likely underestimates the market;
- The 100% continuation rate assumed by the submission does not account for people who stop smoking cessation therapy as a result of a successful quit attempt, adverse events or a return to smoking;
- The growth rate of the OTC Nicotinell® lozenge market was overestimated;
- The assumed conversion factor applied for the OTC market was not split between competitor and sponsor products, which underestimated costs; and
- The assumption that the proportion shifting to nicotine gum and lozenges from varenicline and bupropion would be equal might not be appropriate given the different levels of efficacy and safety between the treatments.

6.60 Furthermore, the DUSC considered the likely place in clinical therapy for the gum and the lozenges is in combination with currently PBS listed smoking cessation therapies. The clinical guidelines recommend combination use to improve smoking cessation. This presented a considerable risk of use beyond the requested restriction.

[1] http://www.racgp.org.au/your-practice/guidelines/smoking-cessation/

6.61 The pre-PBAC response (p3) stated that nicotine gum or lozenges, in combination with nicotine patches, would be equally as effective as varenicline, based on evidence from a Cochrane Collaboration Overview (Cahill et al. 2013). Although no evidence regarding the efficacy or cost-effectiveness of combination therapy compared with varenicline was presented, the sponsor expressed their willingness to work with the Department on combination and extended use.

Quality Use of Medicines

6.62 The submission did not provide any further information regarding the Quality Use of Medicines. The PI for nicotine gum notes that patients should rest the chewing gum between the gum and cheek to allow for optimal absorption of nicotine. It is recommended that patients are instructed on proper nicotine gum usage, and that instructions on proper gum usage are clearly displayed on packaging.

6.63 The DUSC reiterated the importance of the correct use of the nicotine gum and lozenges. The proposed listing for the gum and lozenge to be the sole PBS-subsidised therapy for this condition does not take into account the updated smoking cessation guidelines which encourage health professionals to consider combination NRT for heavy smokers and those who need to have their first cigarette within 30 minutes of waking to enhance efficacy and quit rates from NRT.

7 PBAC Outcome

7.1 The PBAC deferred making a recommendation on whether nicotine gum and lozenges should be listed on the PBS as monotherapies for smoking cessation, pending further clarity on the appropriate use of nicotine gum and lozenges, and its implications for the economic analysis and financial estimates.

7.2 The PBAC recalled that while considering the PBS retention criteria for medicines that were available OTC at its April 2015 Special meeting, the Committee had considered that removal of NRT from the PBS would be a retrograde step in addressing a public health need, noting that retaining NRTs on the PBS for smoking cessation was important "…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."

7.3 The PBAC noted that the requested maximum quantities and the basis of determining the equi-effective doses were based on nicotine gum and lozenges being PBS-listed as monotherapies. However, the PBAC considered that the likely place in clinical therapy for nicotine gum and lozenges would be as combination therapy with long acting forms of currently listed NRTs (nicotine patches, varenicline or bupropion).

- The PBAC considered that combination use was the appropriate place in therapy and that nicotine gum and lozenges would be used as such in practice;

- The PBAC noted that the Royal Australian College of General Practitioners (RACGP)[2] smoking cessation guidelines indicated that combination NRT or varenicline were the most effective forms of pharmacotherapy, encouraging health professionals to consider using combination NRT for smoking cessation;
- The PBAC noted that the merits of combination use were acknowledged in the PSCR and the pre-PBAC response.

7.4 The PBAC noted that the maximum quantity requested in the proposed restriction, based on the mean dosages from the clinical trials, was considerably less than that recommended in the PI for both the lozenge and the gum. The PBAC considered that the proposed maximum quantity was underestimated, given that the requested restrictions require the gum or lozenges to be the sole form of PBS-subsidised smoking cessation medicine permitted in a twelve-month period. Although the PSCR (p3) argued that the increase in quantity may result in wastage and could be a safety issue, the PBAC considered that the proposed maximum quantity would result in under-treatment for some patients and may trigger discontinuation in others.

7.5 The PBAC noted that the Australian Medicines Handbook recommends that the appropriate doses for NRTs were 867 pieces of nicotine gum and 840 pieces of nicotine lozenges, for a 12-week period[3]. The PBAC therefore considered that further deliberation on the most appropriate maximum quantity was required, and advised that the recommendations of the Australian guidelines are taken into account while resolving the disparity between the maximum quantities outlined in the PI, versus those in the proposed PBS restriction. Furthermore, the PBAC advised that the inclusion of dose titration, as described in the PI (i.e. down titration after three months) should be considered while developing the revised restriction criteria.

7.6 The submission nominated nicotine patches as the main comparator for nicotine gum and lozenges. The PBAC considered that this was reasonable, if nicotine gum and lozenges were to be used as monotherapies. The PBAC noted that varenicline was proposed as a relevant comparator for combination use of NRTs in the pre-PBAC response (p3). The PBAC considered that while varenicline was likely to be an appropriate comparator for the use of nicotine gum or lozenges in combination with nicotine patches, nicotine gum or lozenges could be used in combination with varenicline as well in practice. The PBAC noted that no clinical evidence on the potential comparator/s for either of the combinations was presented in the submission or the pre-PBAC response.

7.7 The submission claimed that nicotine lozenge was non inferior to nicotine patches based on three head-to-head trials and a random effects meta-analysis (RR: 0.94, 95% CI: 0.74 to 1.18) (p = 0.629). The PBAC considered that the submission's claim of non-inferiority in relation to comparative efficacy for nicotine lozenges compared with nicotine patches was reasonable.

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[2] http://www.racgp.org.au/your-practice/guidelines/smoking-cessation/

[3] https://amhonline.amh.net.au/chapters/chap-18/nicotine-dependence-drugs/nicotine?menu=hints

7.8 The submission presented an indirect comparison of 56 gum versus control trials and 54 patch versus control trials, claiming that nicotine gum was non-inferior to nicotine patches (RR: 0.91, 95% CI: 0.80 to 1.04) (p = 0.16). Notwithstanding ESC's concerns regarding the upper limit of the 95% CI, which just crosses unity, the PBAC considered that, on balance, the submission's claim of non-inferiority in relation to comparative efficacy for nicotine gum compared with nicotine patches, was reasonable.

7.9 The PBAC also noted that the efficacy of nicotine lozenges and gum significantly improved when used in combination with nicotine patches (Piper, 2009). However, no evidence was provided in the submission about the cost-effectiveness of the combination treatment (see paragraph 7.3).

7.10 The PBAC noted that adverse events experienced by participants receiving nicotine gum or lozenges were similar to those experienced by participants receiving nicotine patches, with hiccups and oral reactions occurring more frequently amongst participants using nicotine gum or lozenges. This was consistent with the PI for both nicotine gum and lozenges. As such, the PBAC considered that the submission's claim of non-inferior safety compared with nicotine patches was reasonable.

7.11 The submission presented a cost-minimisation analysis to estimate the price of nicotine gum and nicotine lozenges, compared with nicotine patches. However, the PBAC considered that there was considerable uncertainty in the estimation of equi-effective doses for both forms using the approach undertaken by the submission, as:

- No strength switching occurred in the trials presented by the submission;
- There was uncertainty around the average number of pieces of lozenges and gum consumed in the trials used to calculate the equi-effective dose in the submission;
- The estimated number of lozenges consumed over 12 weeks was based on applying the adherence rate (67%) in the Piper (2009) trial to the dosage recommended in the PI;
- Trials reporting nicotine gum consumption were associated with significant heterogeneity; and
- The adherence rate (100%) assumed for nicotine patches was not reasonable, as full compliance is unlikely in a clinical setting and did not occur in Piper (2009).

The PBAC therefore advised that the Australian Medicines Handbook[4] recommendations for the appropriate usage of NRT products be utilised in the estimation of equi-effective doses, consistent with its advice regarding the maximum quantity in the proposed PBS restriction (see paragraph 7.5).

7.12 The PBAC noted that the submission did not consider that the PBS subsidy of NRT lozenges or gum would incentivise some groups who may not have otherwise

[4] https://amhonline.amh.net.au/chapters/chap-18/nicotine-dependence-drugs/nicotine?menu=hints

attempted smoking cessation therapy, as (i) nicotine patches are not appropriate for those with contact allergies; and (ii) bupropion and varenicline are not suitable treatment options in pregnancy and might not be appropriate for some people with mental health issues or with other comorbidities.

7.13 The PBAC noted that the submission estimated the cost of listing nicotine gum and lozenges as PBS-subsidised monotherapies was approximately $20 – $30 million over the first five years of listing. The PBAC considered that the financial estimates presented in the submission were underestimated, on account of several inappropriate assumptions as identified by DUSC (see paragraph 6.65). The PBAC considered that combination use of NRTs presented a considerable risk of use beyond the requested restriction, and therefore further clinical evidence and utilisation estimates were warranted before the comparative efficacy and cost-effectiveness of combination use could be appropriately determined by the Committee.

7.14 Acknowledging that smoking cessation was a public health priority area, the PBAC advised that it was willing to consider an alternative approach for the subsidisation of NRT products, pending further clarity on the appropriate use of nicotine gum and lozenges. The PBAC advised that the maximum quantities, economic analysis and utilisation estimates should be revised to account for combination use and resubmitted to the Committee for its consideration.

Outcome:
Deferred

8 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.

9 Sponsor's Comment

The sponsor had no comment.