Pharmaceutical Benefits Scheme

Post-market Review

Post-market Review of medicines for smoking cessation

Report to the PBAC

Report summary and 'options' for PBAC consideration

Contents

Abbreviations

Abbreviation	Full Name / Wording
ACT	Australian Capital Territory
AGREE	Appraisal of Guidelines for Research and Evaluation
AIHW	Australian Institute of Health and Welfare
CER	Cost-effectiveness review
DUSC	Drug Utilisation Sub-Committee
ESC	Economics Sub-Committee
eTG	Electronic Therapeutic Guidelines
ICER	Incremental cost-effectiveness ratio
MBS	Medicare Benefits Schedule
NDSHS	National Drug Strategy Household Survey
NMA	Network meta-analysis
NRT	Nicotine replacement therapy
NSW	New South Wales
NZ	New Zealand
OTC	Over-the-counter
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefits Scheme
PMR	Post-market Review
QALY	Quality-adjusted life-year
RACGP	Royal Australian College of General Practitioners
RCT	Randomised controlled trial
RPBS	Repatriation Pharmaceutical Benefits Scheme
TGA	Therapeutic Goods Administration
ToR	Term of reference
UK	United Kingdom
US	United States
VAR	Varenicline
WA	Western Australia

Acknowledgements

The following organisations and staff have been involved in the preparation of this report:

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Report summary

Background and context

Most tobacco smokers are addicted to nicotine. This addiction is a chronic disease state that is prone to relapses and remissions (1). The majority of people who smoke begin smoking in their youth, and initiation during this period can be particularly detrimental as children and young people who are exposed to nicotine can become addicted at lower and more intermittent levels of tobacco consumption in comparison to adults (2). Nicotine exposure during adolescence may also have damaging and long-term impacts on brain development and can lead to addiction that causes young people to continue smoking for longer and at higher intensities. These factors are strongly associated with tobacco-related disease and premature death (3).

According to the 2019 National Drug Strategy Household Survey (NDSHS) conducted by the Australian Institute of Health and Welfare (AIHW), 11.0% of Australians aged 14 years and over smoked daily, a significant decrease from 24.3% in 1991. Despite the long-term progress Australia has made in reducing smoking prevalence, tobacco remains the leading cause of death and disability in Australia. In 2015, cigarette smoking was responsible for 9.3% of the total burden of disease and injury, and more than 1 in every 10 (21,000) deaths (4).

Tobacco use compounds health and social inequalities and is a major contributor to poorer health status in socioeconomically disadvantaged populations. The most recent available estimates of the overall social (including health) costs of tobacco use in Australia were $137 billion in 2015-16, including $19.2 billion in tangible costs and $117.7 billion in intangible costs (5).

There are currently three pharmacological interventions for smoking cessation available on the Pharmaceutical Benefits Scheme (PBS): nicotine replacement therapy (NRT) (in patch, gum, and lozenge form), varenicline and bupropion.

In the financial year for 2019/2020;

- 1.2% of the Australian population (265,544 people) were supplied 542,492 prescriptions for PBS-subsidised smoking cessation therapies.
- Three people per 1,000 in the Australian population (65,543 people) made their first ever attempt at quitting with a PBS-subsidised smoking cessation therapy.
- $36 million in R/PBS benefits were paid for smoking cessation therapies.

In July 2017, the Pharmaceutical Benefits Advisory Committee (PBAC) deferred a major submission for the listing of NRT in the form of gum and lozenges (2mg and 4mg strengths) on the PBS. The PBAC noted that the efficacy of nicotine lozenges and gum significantly improved when used in combination with nicotine patches, but that no evidence was provided in the submission about the cost-effectiveness of combination NRT.

In March 2018, the PBAC recommended the listing of nicotine gum and lozenges as monotherapies on the PBS for treating nicotine dependence. The PBAC considered that a broader review of PBS-listed nicotine dependence treatments, in the context of the current clinical guidelines, would help inform whether the current subsidy arrangements should be altered to better support smoking cessation.

The Post-market Review (PMR) ("the Review") of medicines for smoking cessation was approved by the Minister for Health on 18 September 2019.

Review terms of reference

The PMR of medicines for smoking cessation consisted of four terms of reference (ToRs).

1. Collate the current clinical guidelines for medicines for smoking cessation and compare these to the Therapeutic Goods Administration (TGA) and PBS restrictions for these medicines.
2. Review the utilisation of PBS-listed medicines for smoking cessation including but not limited to patient demographics, time on treatment, and the proportion using PBS-subsidised combination treatment.
3. Review the efficacy and safety of NRT, varenicline and bupropion for smoking cessation including combination therapies not currently PBS-subsidised.
4. Subject to the findings of ToRs 1, 2 and 3, review the cost-effectiveness of medicines for smoking cessation.

Structure and approach to the report

This report is presented in several parts, as briefly outlined below. The report has been structured in this way to address the ToRs of the Review.

Background: Provides the context for the Review, a brief description of nicotine dependence and the listing history for PBS-listed medicines for smoking cessation.

Report summary: Provides a summary of the key findings from the Review and the 'options' for the PBAC raised by the reference group

Section 1 – ToR 1: Collates the current clinical guidelines for medicines for smoking cessation and compares these to the TGA and PBS restrictions for these medicines.

Section 2 – ToR 2: Reviews the utilisation of PBS-listed medicines for smoking cessation including but not limited to patient demographics, time on treatment, and the proportion using PBS-subsidised combination treatment.

Section 3 – ToR 3: Reviews the efficacy and safety of NRT, varenicline and bupropion for smoking cessation including combination therapies not currently PBS-subsidised.

Section 4 – ToR 4: Provides a cost-effectiveness review of specified combinations of smoking cessation medicines and estimates for the PBS.

Research questions were developed for each ToR under the guidance of the review reference group. The research questions examined for each ToR are presented under each ToR addressing the key findings below. The methodology for each ToR is presented in the relevant section of the report.

Stakeholder consultation

Opportunities for stakeholder consultation throughout the PMR included:

- Public consultation on the draft ToRs: closed on 25 November 2019. Except where requested otherwise, submissions are published on the Review's website.

- Public submissions to the Review: closed on 1 May 2020. Except where requested otherwise, submissions are published on the [Review's website.](#)
- A stakeholder forum held via webinar on 3 December 2020. The stakeholder forum summary is available on the [Review's website.](#)
- Public consultation on the draft report: closed on 2 July 2021.

Key Review findings

ToR 1: Comparison of prescribing restrictions and clinical guidelines

> *Collate the current clinical guidelines for medicines for smoking cessation and compare these to the TGA and PBS restrictions for these medicines*

1.1 Identify and compare relevant clinical guidelines including Australian, health service and international guidelines

- Twelve national (Australian) and four international guidelines were identified.
- National guidelines included three country-level guidelines from the Royal Australian College of General Practitioners (RACGP), the electronic Therapeutic Guidelines (eTG) and Department of Health and Ageing, four state-level Department of Health guidelines (Quit for New Life, New South Wales [NSW] Health, Queensland Health and Western Australia [WA] Department of Health[1]), three additional guidelines by Alfred Health (June 2017 and Aug 2017 updated) and the Royal Women's Hospital, Victoria (referred herein as the Women's). The Cancer Council Victoria published a comprehensive review of smoking cessation, and whilst not a clinical guideline per se, has been included as a key document.
- The international guidance documents included guidelines from New Zealand (NZ), the United Kingdom (UK), Canada and the United States (US).
- The quality grading of evidence and strength of the guidelines were assessed using the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument. Two national (RACGP and Cancer Council Victoria) and two international guidelines (NZ and UK) were assessed as higher quality. Several other national guidelines were also considered very good quality including Australian Capital Territory (ACT) Health, WA Health[1], NSW Health, Alfred Health (updated guidelines – 2020), eTG, Department of Health and Ageing, and the Women's, along with the remaining two international guidelines (Canada and US).
- Several similarities were apparent between the national and international guidelines as follows:
    - Approach to smoking cessation, including choice of pharmacotherapy, should be tailored to the patient including consideration of nicotine dependence, clinical suitability, and patient preference.
    - Varenicline was considered more effective than NRT monotherapy and bupropion, and at least equivalent to combination NRT.
    - Combination NRT was considered more effective than NRT monotherapy or bupropion.
    - Any pharmacotherapy combined with behavioural support was considered more effective than pharmacotherapy alone.

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[1] The Government of Western Australia, Department of Health, 'Guidelines to manage nicotine withdrawal and cessation support in nicotine dependent patients' (2020) were rescinded on 30 June 2021.

- o Referral to a specialised counselling service (e.g., Quitline or similar trained smoking cessation counsellors) was recommended.
- o Using appropriate dosing for NRT, proportional to the level of nicotine dependence, was important, as was up-titrating the dose (including the option of double patching (i.e., adding an extra patch) if there was limited response. Under-dosing was considered common and associated with risk of not achieving cessation.
- o NRT should be used for 8-12 weeks, varenicline for 12 weeks and bupropion for at least seven weeks. Some national and international guidelines allowed for a second course of NRT or varenicline, but not bupropion, to prevent relapse, or if complete abstinence was not achieved.
- o NRT was considered appropriate for use in adolescents > 12 years, patients with stable cardiovascular disease (CVD) and pregnant women (although preference was to achieve smoking cessation without use of NRT in pregnant women).
- There were some discrepancies between various guidelines, particularly around the use of combinations of NRT, varenicline and bupropion. Some guidelines recommended some or all combinations, but UK guidelines specifically recommended against the combination of varenicline and bupropion.
- Differences were also seen in how nicotine dependence was assessed, particularly in relation to dosing of NRT. However, there was agreement on the overall principle that increased reliance on nicotine (whether measured by time to first cigarette, or number of cigarettes per day, or a combination of these) should trigger use of higher doses of NRT at the time of quitting.

1.2 Compare TGA indications and PBS restrictions to the most clinically relevant clinical guidelines identified in 1.1

- All guideline recommendations were within TGA indications for all therapies under consideration (NRT, bupropion and varenicline).
- The PBS listing for NRT does not allow for the use of two forms of NRT at once (i.e., no combination therapy) which is inconsistent with all guidelines reviewed and TGA-approved dosing of NRT.
- The PBS listings for varenicline and bupropion were consistent with guideline recommendations for use of these drugs as monotherapy. However, the PBS restriction requiring a six-month gap between initiating sequential quit attempts was not reflected in the guidelines.
- The PBS listings for varenicline and bupropion are inconsistent with the guidelines that support the use of these therapies in combination with another smoking cessation therapy. However, there was also discrepancy between guidelines as to whether these medications should be used in combination. The TGA indications do not preclude combination therapy.
- 'Cut-down to quit' and pre-quit use of NRT were TGA-approved and recommended strategies in most guidelines. This approach was not explicitly considered in the PBS restrictions, and may not be adequately accounted for within the allowable quantities and repeats.
- Current PBS prescriptions for NRT do not allow for extension of a course of therapy beyond 12 weeks although several guidelines recommended extension of therapy if needed. The exception to this was for the Aboriginal and Torres Strait Islander population

where up to 24 weeks of PBS-subsidised NRT were allowed. No guideline distinguished between the Aboriginal and Torres Strait Islander population and the general population regarding extension of therapy.

- The allowable quantities for NRT patches in the current PBS restrictions do not account for 'double-patching' although several guidelines suggested that this may be useful for heavily dependent smokers.
- Higher strength NRT patches were PBS-listed for Aboriginal and Torres Strait Islanders but lower strength patches were not. This was inconsistent with the guidelines which do not indicate any evidence-based requirement for only higher strengths for Aboriginal and Torres Strait Islanders.

1.3 Review the most commonly recommended clinical assessment measure used to evaluate the severity of nicotine dependence

- Under-dosing of NRT was considered common and assessment of nicotine dependence was recommended prior to prescribing of pharmacotherapy.
- Clinical guidelines used a range of instruments to assess nicotine dependence including:
  - The Fagerström test which tests psychological and physiological dependence
  - A subset of two of the Fagerström questions – 'how long until you have your first cigarette after waking?', and 'how many cigarettes a day do you smoke?'
  - Simply asking 'how many cigarettes a day do you smoke?'

1.4 Stakeholder views (forum and public consultations)

Initial consultation feedback recommended that health service guidelines be included in the evaluation of ToR 1, in addition to national and international guidelines. Based on this feedback several health service guidelines, including those published by Alfred Health and the Royal Women's Hospital (Victoria), have been included in the evaluation of ToR 1. A review published by the Cancer Council Victoria was included as a 'key document.'

Stakeholders generally considered that the PBS restrictions should align with current clinical guidelines (such as the RACGP's 'Supporting smoking cessation: A guide for health professionals').

Stakeholders considered it important to ensure that the availability of medicines for smoking cessation are subsidised consistent with clinical guidelines to support people to quit smoking.

ToR 2: Analysis of utilisation of PBS-listed medicines for smoking cessation

Review the utilisation of PBS-listed medicines for smoking cessation including but not limited to patient demographics, time on treatment, and the proportion using PBS-subsidised combination treatment.

2.1 Describe the overall trends in the utilisation and cost of smoking cessation medicines in Australia

In the financial year 2019/2020:
- There were 542,492 prescriptions dispensed for PBS-subsidised smoking cessation therapies at a cost to the government of AUD 36 million (PBS benefits paid).

- Varenicline was the most utilised smoking cessation therapy with 303,681 PBS prescriptions dispensed (56% of the total market) followed by NRT with 233,544 PBS prescriptions (43% of the total market) and bupropion with 5,267 PBS prescriptions (<1% of the total market).
- PBS use of NRT represented 7% of all NRT use in Australia during 2019, suggesting that the majority of NRT products are obtained over-the-counter (OTC). NRT patches accounted for 94% of all NRT products subsidised under the PBS, while the majority of NRT products sold OTC were nicotine gums.

2.2 Determine the prevalent and incident populations treated with PBS-listed medicines for smoking cessation

- 1.2% of the Australian population (N=265,544) were supplied PBS smoking cessation therapy in 2019/2020.
- 0.3% of the Australian population (N=65,543) made their first ever attempt at quitting with PBS-subsidised smoking cessation therapy in 2019/2020.

2.3 Provide the most recent statistics on the prevalence of smoking in Australia

The smoking rates differed widely between different sub-populations:
- In 2019, there were an estimated 2.9 million current smokers aged 18+ in Australia representing 14.7% from the overall population aged 18+ in Australia;
- In 2019, the rate of Aboriginal and Torres Strait Islander people aged 15+ who are current smokers was 41.4%, which was 2.8 times higher in comparison to the overall population aged 18+ in Australia;
- In 2018, at least 75% of non-Indigenous prison entrants aged 18-44 years were current smokers, and at least 79% of Aboriginal and Torres Strait Islander prison entrants aged 18-44 were current smokers;
- In 2018, 9% of women smoked in the first 20 weeks of pregnancy;
- People with self-reported mental illness (depression, anxiety disorder, schizophrenia, bipolar disorder, an eating disorder, or other mental illness) were almost twice as likely to be current smokers compared to people without mental illness (24% vs 13% in 2019).

2.4 Prevalence of smoking cessation therapies under the PBS in specific populations

Of the 265,544 people who received PBS-subsidised smoking cessation therapy in 2019:
- 40% also had mental illness, as measured by antipsychotic and antidepressant use
- 18% were women of child-bearing age (aged 15 to 44 years)
- 16% also had a smoking related illness, as measured by use of medicines for airways disease
- 10% were Aboriginal and Torres Strait Islanders, identified by the following criteria – a supply of prescriptions under the 'Closing the Gap (CTG) Co-Payment Measure Program,' or utilisation of Indigenous-specific Medicare Benefits Schedule (MBS) items, or Voluntary Indigenous Identifier
- 1% were at risk of alcohol abuse, as measured by use of medicines for alcohol dependence.

2.5 Estimates of specific populations of interest with access to smoking cessation therapies under the PBS

In calendar year 2019, based on PBS utilisation and published literature, it is estimated that:
- 10% of all current smokers aged 18 years and over in Australia received smoking cessation therapies under the PBS;
- 1% of all Australian women of child-bearing age (aged 15 to 44 years) received smoking cessation therapies under the PBS;
- 6% of the Aboriginal and Torres Strait Islander population aged 18+ in Australia received smoking cessation therapies under the PBS.

2.6 Number of therapies and length of treatment with smoking cessation medicines

Based on an analysis of PBS data, there were 740,082 people who initiated a PBS-subsidised smoking cessation therapy for the first time between 1/07/2010 and 30/06/2015. The following results are based on this initiating cohort who were followed for 5 years:
- The median duration of the first treatment episode was 28 days for bupropion and 42 days for NRT and varenicline;
- 60% of people in this cohort made only one attempt to quit smoking;
- Overall, people had on average 1.7 separate treatment episodes with smoking cessation therapies with an average break of 15 months between attempts.

2.7 Use of counselling services

According to the AIHW, NDSHS (2019), 1.8% of current smokers aged 14 years and over (i.e., approximately 52,000 people) contacted Quitline in 2019.

The survey suggests low uptake of counselling services compared to the population accessing PBS medicines for smoking cessation (265,544 people in 2019/2020).

2.8 Consistency with PBS restrictions

Among people supplied their first ever PBS-subsidised smoking cessation therapy in financial year 2018/2019:
- 88% of NRT users complied with the PBS restriction in that they received a maximum of 12 weeks of PBS-subsidised NRT per year. Analysis of all first ever NRT initiators in 2018/2019 showed that:
  - 60% received only one prescription for NRT which covers 4 weeks of therapy,
  - 17% received 2 prescriptions for NRT which covers 8 weeks of therapy,
  - 12% received 3 prescriptions for NRT which covers 12 weeks of therapy.
- 98% of varenicline users complied with the PBS restriction requirement in that they received a maximum of 24 weeks supply of PBS-subsidised varenicline per 12-month period. Analysis of the type of packs dispensed to first ever initiators to varenicline in 2018/2019 showed that:
  - 56% of initiators had only a starter pack (duration of 4 weeks),
  - 24% had a starter pack plus a continuation pack or a starter pack plus two completion packs (duration of 12 weeks)
  - 1% had a starter pack plus a continuation pack and three completion packs (duration of 24 weeks).

- 91% of bupropion users complied with the PBS restriction requirement in that they received a maximum of 9 weeks supply of PBS-subsidised bupropion per year. Analysis of all first ever bupropion initiators in 2018/2019 showed that:
    - 45% of initiators had only a starter pack (duration of 2 weeks),
    - 20% of initiators completed up to 8 weeks of therapy.

There was no significant difference in duration of NRT therapy between Aboriginal and Torres Strait Islander people and non-Indigenous people who initiated NRT for the first time in 2018/2019. This is despite Aboriginal and Torres Strait Islander people being allowed an additional 12-week course per 12-month period (up to 24 weeks) of PBS-subsidised NRT in the form of 25 mg/16 hour patch, 21 mg/24 hour patch, lozenges, and gum. However, this does not include data on NRT therapies provided by Aboriginal Health Services that are participating in the Remote Area Aboriginal Health Services (RAAHS) program.

2.9 Stakeholder views (forum and public consultations)

Stakeholders considered that the cost of OTC NRT can be a significant barrier for many people, particularly those from populations with higher rates of smoking such as lower socioeconomic groups, Aboriginal and Torres Strait Islander people, and people with a mental illness. Stakeholders considered that financial cost was an important factor in unsuccessful quit attempts, particularly for non-PBS-subsidised NRT therapies and when therapy was required for longer than is available on the PBS. Table 2 of the Background report (p. 12) provides indicative costs for OTC and PBS smoking cessation therapies.

One stakeholder noted the 2018 evaluation of the Tackling Indigenous Smoking (TIS)[2] program found that the high cost of NRTs that are not available on the PBS was a significant barrier to NRT access for Aboriginal and Torres Strait Islander people.

Stakeholders also noted that lack of access to smoking cessation medicines is particularly important for people in regional and remote areas, including Aboriginal and Torres Strait Islander people.

Some clinicians noted that in their experience therapies are being used for longer than indicated to allow people additional time to abstain, and often in combination (short + long acting NRT combination, varenicline + NRT) to manage withdrawal and cravings.

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[2] Tackling Indigenous Smoking Program Final Evaluation Report. Prepared for the Australian Government Department of Health July 2018 https://www.health.gov.au/sites/default/files/tackling-indigenous-smoking-program-final-evaluation-report.pdf.

ToR 3: Efficacy and safety of nicotine replacement therapy, varenicline and bupropion for smoking cessation including combination therapies

Review the efficacy and safety of nicotine replacement therapy, varenicline and bupropion for smoking cessation including combination therapies not currently PBS-subsidised.

In the evidence reviewed, the efficacy of smoking cessation therapies was based on long-term (i.e., 6 months or more) smoking cessation rates unless otherwise indicated. Biochemically validated and continuous abstinence rates were prioritised over other measures. For safety and tolerability outcomes, key adverse events from studies with follow-up of any length are presented, where reported. A qualitative or narrative synthesis of the data from the literature review was conducted along with quantitative analysis if possible. Where supplemental evidence was found, the meta-analysis reported in the Cochrane Reviews (relative risk using fixed-effect models) was re-analysed where possible using Review Manager 5.4 software and updated using random-effect models, with outcomes reported as both absolute and relative effects.

3.1 Monotherapy in the general population

Summarise the comparative efficacy and safety of all PBS-listed smoking cessation therapies as monotherapy and compare this to evidence already considered by the PBAC for each smoking cessation therapy

3.1.1 Bupropion

Treatment-naïve population

- Bupropion was superior to placebo in terms of efficacy, with a significantly higher incidence of adverse events, psychiatric adverse events, and discontinuation due to adverse events in the bupropion arm. This is consistent with the evidence previously considered by the PBAC.
- No statistically significant differences in smoking cessation rates, adverse events, serious adverse events, and discontinuation due to adverse events were shown between bupropion and NRT (either as patch, lozenge, or choice of NRT). This is consistent with the evidence previously considered by the PBAC to support non-inferiority.

Comparison	Included studies	Summary of evidence
Treatment-naïve population		
Bupropion vs placebo	• Howes (2020)[1] • Benowitz (2018)[2]	• <u>Efficacy:</u> Statistically significant based on RR (in favour of bupropion). • <u>Safety:</u> Statistically significant based on RR (any AEs, psychiatric AEs, discontinuation due to AEs; higher in bupropion); not statistically significant based on RR (SAEs).
Bupropion vs NRT (either as patch, lozenge, or choice of NRT)	• Howes (2020)[1] • Benowitz (2018)[2]	• <u>Efficacy:</u> Not statistically significant based on RR. • <u>Safety:</u> Not statistically significant based on RR (any AEs, SAEs, discontinuation due to AEs).

Abbreviations: AEs = adverse events; NRT = nicotine replacement therapy; RR = risk ratio, RD = risk difference; SAEs = serious adverse events.
Notes:
1 Cochrane Review.
2 Supplemental evidence (RCT).

Treatment-experienced population

- Bupropion has not previously been considered by the PBAC for treatment-experienced patients.
- No evidence was identified comparing bupropion with placebo as relapse prevention in abstainers who completed a 9-week course of initial bupropion monotherapy treatment (PBS-listed treatment duration). In other studies, irrespective of treatment duration, there were no statistically significant differences between bupropion and placebo in terms of efficacy as a relapse prevention treatment in abstainers. The adverse events reported were consistent with those expected of bupropion.
- There were no statistically significant differences between bupropion and placebo in terms of efficacy for use as retreatment in non-abstainers when based on risk ratio, noting that the results were significant when based on risk difference. While a significantly higher proportion of patients in the bupropion arm experienced adverse events compared to patients in the placebo arm, there were no statistically significant differences in serious adverse events or discontinuation due to adverse events.

Comparison	Included studies	Summary of evidence
Treatment-experienced population (relapse prevention treatment in abstainers)		
Bupropion vs placebo	• Livingstone-Banks (2019)[1]	• <u>Efficacy</u>: Not statistically significant based on RR. • <u>Safety</u>: AEs reported were consistent with those expected of bupropion.
Treatment-experienced population (retreatment in non-abstainers)		
Bupropion vs placebo	• Gonzales (2001)[2] • Selby (2003)[2]	• <u>Efficacy</u>: Not statistically significant based on RR but significant based on RD[3]. • <u>Safety</u>: Statistically significant based on RR and RD (any AEs; higher in bupropion); Not statistically significant based on RR and RD (SAEs, discontinuation due to AEs).

Abbreviations: AEs = adverse events; RR = risk ratio, RD = risk difference; SAEs = serious adverse events.

Notes:

1 Cochrane Review. Of the studies identified by Livingstone-Banks et al. (2019), Croghan et al. (2007) was the only study that compared bupropion with placebo in patients who achieved abstinence after initial treatment with bupropion monotherapy; the other studies provided either NRT patches or bupropion plus NRT patches in the initial treatment phase. The key limitation of Croghan et al. (2007) was related to the duration of bupropion monotherapy administered in the initial treatment phase (3 months versus 9 weeks on the PBS) and the relapse prevention phase (9 months).

2 Included in Cochrane Review by Howes et al. (2020).

3 Not statistically significant based on risk ratio but significant based on risk difference (RR = 2.31, 95%CI: 0.90, 5.92; RD = 0.06, 95%CI: 0.02, 0.10).

3.1.2 Varenicline

Treatment-naïve population

- Varenicline was shown to be superior to placebo in terms of efficacy based on long-term smoking cessation rates. In terms of safety, a significantly higher incidence rate of adverse events (nausea, insomnia, abnormal dreams, headache) and serious adverse events was observed for varenicline, but the results for headache and serious adverse events were no longer statistically significant in the updated re-analysis of this review (based on risk ratio). There were no statistically significant differences between varenicline and placebo for depression, suicidal ideation, neuropsychiatric serious adverse events, and cardiac serious adverse events. This is consistent with the evidence previously considered by the PBAC, noting the updated safety data for headache and serious adverse events.

- Varenicline was shown to be superior to bupropion in terms of efficacy. No statistically significant differences were found in adverse events, psychiatric adverse events, serious adverse events, and discontinuation due to adverse events between varenicline and bupropion. This is consistent with the evidence previously considered by the PBAC.

Comparison	Included studies	Summary of evidence
Treatment-naïve population		
Varenicline vs placebo	- Cahill (2016)[1] - Lerman (2015)[2] - Littlewood (2017)[2] - Benowitz (2018)[2] - Hurt (2018)[2] - Mercie (2018)[2] - Windle (2018)[2] - Ashare (2019)[2] - Chen (2020)[2]	Efficacy: Statistically significant based on RR and RD (in favour of varenicline). Safety: Statistically significant based on RR and RD (nausea, insomnia, abnormal dreams; higher in varenicline); Not statistically significant based on RR (depression, suicidal ideation, serious AEs including neuropsychiatric and cardiac), but significant based on RD (headache).
Varenicline vs bupropion	- Howes (2020)[1] - Benowitz (2018)[2]	- Efficacy: Statistically significant based on RR and RD (in favour of varenicline). - Safety: Not statistically significant based on RR and RD (any AEs, psychiatric AEs, SAEs, discontinuation due to AEs).

Abbreviations: AEs = adverse events; RR = risk ratio, RD = risk difference; SAEs = serious adverse events.
Notes:
1 Cochrane Review.
2 Supplemental evidence (RCT).

Treatment-experienced population

- Varenicline was shown to provide a statistically significant improvement in efficacy compared with placebo as a relapse prevention treatment in abstainers. This is largely based on, and thus is consistent, with the evidence previously considered by the PBAC. The adverse events reported were consistent with those expected of varenicline.

- Varenicline was shown to be superior to placebo in terms of efficacy as retreatment in non-abstainers. A significantly higher proportion of patients in the varenicline arm experienced nausea and abnormal dreams compared to patients in the placebo arm, while there were no statistically significant differences between the two treatment arms for insomnia, headache, depression, serious adverse events, and cardiac serious adverse events. This is consistent with the evidence previously considered by the PBAC. It was noted that one study identified required patients to have had previously taken varenicline for two or more weeks, with the last dose taken ≥3 months before screening.

Comparison	Included studies	Summary of evidence
Treatment-experienced population (relapse prevention treatment in abstainers)		
Varenicline vs placebo	• Livingstone-Banks (2019)[1] • Schnoll (2019)[2]	• <u>Efficacy</u>: Statistically significant based on RR (in favour of varenicline). <u>Safety</u>: AEs reported were consistent with those expected of varenicline.
Treatment-experienced population (retreatment in non-abstainers)		
Varenicline vs placebo	• Cahill (2016)[1]	• <u>Efficacy</u>: Statistically significant based on RR (in favour of varenicline). • <u>Safety</u>: Statistically significant based on RR (nausea, abnormal dreams; higher in varenicline); Not statistically significant based on RR (insomnia, headache, depression, SAEs including cardiac).

Abbreviations: AEs = adverse events; RR = risk ratio, RD = risk difference; SAEs = serious adverse events.
Notes:
1 Cochrane Review.
2 Supplemental evidence (RCT).

3.1.3 Nicotine replacement therapy

Treatment-naïve population

- NRT patches were shown to be superior to placebo in terms of efficacy, noting that similar results were observed for NRT gum or lozenges (as monotherapy) versus placebo. There was a significantly higher incidence of palpitations, tachycardia, or chest pains with NRT (various formulations) compared with placebo. This is consistent with the evidence previously considered by the PBAC.
- NRT patches were shown to be inferior to varenicline in terms of efficacy based on a statistically significant difference in point prevalence abstinence at 24 weeks, in favour of varenicline. In terms of safety, there were no statistically significant differences in side effects (including neuropsychiatric and cardiovascular safety profile) between the two treatment arms. This is consistent with the evidence previously considered by the PBAC.
- No statistically significant differences in smoking cessation rates, serious adverse events, and withdrawals due to treatment were shown between NRT lozenges or gum and NRT patches. This is largely based on, and thus is consistent with, the evidence previously considered by the PBAC to support non-inferiority.

Comparison	Included studies	Summary of evidence
Treatment-naïve population		
NRT (patch, gum, or lozenge) vs placebo	• Hartmann-Boyce (2018)[1] • Benowitz (2018)[2]	• <u>Efficacy</u>: Statistically significant based on RR and RD (in favour of NRT). • <u>Safety</u>: Statistically significant based on OR (palpitations, tachycardia, chest pains; higher in NRT).
NRT patch vs varenicline	• Cahill (2016)[1] • Lerman (2015)[2] • Tulloch (2016)[2] • Rohsenow (2017)[2] • Benowitz (2018)[2]	• <u>Efficacy</u>: Statistically significant based on RR and RD (in favour of varenicline). • <u>Safety</u>: Not statistically significant (AEs incl. neuropsychiatric and cardiovascular safety)[3].
NRT (gum or lozenge) vs NRT patch	• Lindson (2019)[1]	• <u>Efficacy</u>: Not statistically significant based on RR. • <u>Safety</u>: Not statistically significant based on RR (SAEs, withdrawal due to treatment).

Abbreviations: AEs = adverse events; NRT = nicotine replacement therapy; OR = odds ratio; RR = risk ratio, RD = risk difference; SAEs = serious adverse events.
Notes:
1 Cochrane Review.
2 Supplemental evidence (RCT).
3 Qualitative synthesis.

Treatment-experienced population

- NRT has not previously been considered by the PBAC for treatment-experienced patients.
- There were no statistically significant differences between NRT (either as gum or inhaler) and placebo in terms of efficacy as a relapse prevention treatment in abstainers. The adverse events reported were consistent with those expected of NRT. No evidence was identified comparing NRT monotherapy (either as patch, gum, or lozenge) with placebo in patients who achieved abstinence after initial treatment with NRT monotherapy using the same formulation.
- The results of Gourlay et al. (1995), based on continuous abstinence rate, demonstrated no statistically significant difference between NRT patches and placebo in non-abstainers as retreatment at 6 months. However, there was a statistically significant improvement in smoking cessation rates using NRT patches based on 28-day point prevalence abstinence (RR: 2.49; 95% CI: 1.11, 5.57) at this point in the study by Gourlay et al. (1995) only. In terms of safety, there were no statistically significant differences between the two treatment arms for palpitations, tachycardia, or chest pains. It was noted that the quit rates were low in both groups with either definition of abstinence. In terms of safety, there were no statistically significant differences between the two treatment arms for palpitations, tachycardia, or chest pains.

Comparison	Included studies	Summary of evidence
Treatment-experienced population (relapse prevention treatment in abstainers)		
NRT (gum or inhaler) vs placebo	• Livingstone-Banks (2019)[1]	• Efficacy: Not statistically significant based on RR. • Safety: AEs reported were consistent with those expected of NRT.
Treatment-experienced population (retreatment in non-abstainers)		
NRT (patch) vs placebo	• Gourlay (1995)[2]	• Efficacy: Not statistically significant based on RR and RD. • Safety: Not statistically significant based on RR and RD (palpitations, tachycardia, chest pains).

Abbreviations: AEs = adverse events; OR = odds ratio; RR = risk ratio, RD = risk difference.

Notes:

1 Cochrane Review. None of the studies identified by Livingstone-Banks et al. (2019) compared NRT monotherapy (either as patch, gum, or lozenge) with placebo in patients who achieved abstinence after initial treatment with NRT monotherapy using the same formulation. In Covey et al. (2007), patients were provided bupropion plus NRT patches in the initial treatment phase while patients were provided NRT inhaler in Croghan et al. (2007).

2 Included in Cochrane Review by Hartmann-Boyce et al. (2018).

3.2 Combination therapy in the general population

Summarise the comparative efficacy and safety of PBS-listed treatments when used as combination therapy

Combination therapies for smoking cessation have not been previously considered by the PBAC. In March 2018, the PBAC noted that the latest clinical guidelines encouraged health professionals to consider recommending the use of combination NRT (e.g., NRT patch with NRT gum or lozenges).

3.2.1 Combination NRT

Treatment-naïve population

- Combination NRT (patch + lozenge, patch + lozenge and gum) was shown to be superior to placebo in terms of efficacy, noting the results of the updated re-analysis for NRT patch + lozenge was statistically significant based on risk ratio but not risk difference. There were no statistically significant differences in smoking cessation rates between NRT patch + gum or NRT patch + inhalator and placebo. The non-significant result of NRT patch + gum was likely due to study design issues, such as small sample size, leading to insufficient power to detect a modest treatment effect with reasonable certainty. The incidence of adverse events comparing combination NRT with placebo was not synthesised quantitatively. However, based on one randomised controlled trial (RCT), which did not detect a statistically significant difference in efficacy, no statistically significant differences between NRT patch + lozenge and placebo were reported in terms of any adverse events and serious adverse events.
- Combination NRT was shown to be superior to NRT monotherapy (patch or fast-acting) in terms of efficacy. In terms of safety, there were no statistically significant differences in cardiac adverse events, serious adverse events, or withdrawals due to treatment. Additional subgroup analyses were conducted during the review to determine the comparative effectiveness of the different types of combination NRT formulations:

- Combination NRT versus NRT patches: for this comparison NRT patch + lozenge and NRT patch + gum was shown to provide a significantly higher rate of smoking cessation compared to NRT patches alone. There were no statistically significant differences observed for the other types of combination NRT formulations (patch + nasal spray, patch + inhaler, patch + oral spray) when compared to NRT patches alone.
- Combination NRT versus fast-acting NRT; for this comparison only NRT patch + lozenge was shown to provide a significantly higher rate of smoking cessation compared to fast-acting NRT alone. There were no statistically significant differences observed for the other types of combination NRT formulations (patch + gum, patch + nasal spray, patch + inhaler) when compared to fast-acting NRT alone.

- Combination NRT (patch + lozenge) was shown to be inferior to varenicline in terms of efficacy with no statistically significant differences in terms of safety based on one direct RCT. There was a statistically significant difference in point prevalence abstinence at 6 months, in favour of varenicline, while there were no statistically significant differences across the key adverse events between the two treatment arms, except for nausea and vivid dreams which were significantly higher in the varenicline arm. However, the results of the network meta-analysis (NMA) by Cahill et al. (2013) demonstrated no statistically significant difference in smoking cessation rates between combination NRT and varenicline, although the results numerically favoured varenicline. The types of formulations used in the combination NRT treatment arm were clinically heterogeneous and the results of the NMA should be interpreted with caution due to potential biases and uncertainties arising from heterogeneity and inconsistent outcomes between studies.[3]
- Combination NRT was shown to be superior to bupropion in terms of efficacy based on the results of the NMA by Cahill et al. (2013) (no direct RCT was identified for this comparison). Similarly, this result should be interpreted with caution due to the general limitations of NMA and the types of formulations used in the combination NRT treatment arm were clinically heterogeneous.

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[3] The efficacy of combination NRT relative to varenicline was investigated further as part of the ToR 4 report. For further information refer to p.43 of 'ToR 4: Cost-effectiveness review of specified combinations of smoking cessation medicines and estimates for the Pharmaceutical Benefits Scheme.'

Comparison	Included studies	Summary of evidence
Treatment-naïve population		
Combination NRT[1] vs placebo	• Hartmann-Boyce (2018)[6] • Chen (2020)[7]	• <u>Efficacy</u>: Statistically significant based on RR (in favour of patch+lozenge[8] and patch+lozenge and gum) but not RD (patch+lozenge[8]); not statistically significant based on RR (patch+gum and patch+inhaler). • <u>Safety</u>: Not statistically significant based on RR and RD (any AEs, SAEs; NRT patch+lozenge).
Combination NRT[2] vs NRT monotherapy (patch)	• Lindson (2019)[6] • Leung (2019)[7]	• <u>Efficacy</u>: Statistically significant based on RR and RD (in favour of patch+lozenge and patch+gum); Not statistically significant (patch+nasal spray, patch+inhaler and patch+oral spray). • <u>Safety</u>: Not statistically significant based on RR (SAEs, withdrawal due to treatment), and RD (cardiac AEs).
Combination NRT[3] vs NRT monotherapy (fast-acting)	• Lindson (2019)[6]	• <u>Efficacy</u>: Statistically significant based on RR (in favour of patch+lozenge); Not statistically significant based on RR (patch+gum, patch+nasal spray and patch+inhaler). • <u>Safety</u>: Not statistically significant based on RR (SAEs, withdrawal due to treatment).
Combination NRT[4] vs varenicline	• Chen (2020)[7]	• <u>Efficacy</u>: Statistically significant based on RR and RD (in favour of varenicline). • <u>Safety</u>: Statistically significant based on RR and RD (nausea, vivid dreams; higher in varenicline); Not statistically significant based on RR and RD (vomiting, headache, insomnia, irregular heartbeat, SAEs).
Combination NRT[5] vs varenicline	• Cahill (2013)[6]	• <u>Efficacy</u>: Not statistically significant based on OR. • <u>Safety</u>: No safety comparison was conducted by the authors.
Combination NRT[5] vs bupropion	• Cahill (2013)[6]	• <u>Efficacy</u>: Statistically significant based on OR (in favour of combination NRT). • <u>Safety</u>: No safety comparison was conducted by the authors.

Abbreviations: AEs = adverse events; NRT = nicotine replacement therapy; OR = odds ratio; RR = risk ratio, RD = risk difference; SAEs = serious adverse events.

Notes:

1 Combination NRT administered either as patch+lozenge, patch+gum, patch+inhaler, or patch+lozenge and gum.

2 Combination NRT administered either as patch+lozenge, patch+gum, patch+inhaler, patch+nasal spray, or patch+oral spray.

3 Combination NRT administered either as patch+lozenge, patch+gum, patch+inhaler, or patch+nasal spray.

4 Combination of NRT patches and lozenges.

5 The types of formulations used in the combination NRT treatment arm were clinically heterogeneous.

6 Cochrane Review.

7 Supplemental evidence (RCT).

8 Statistically significant based on risk ratio but not significant based on risk difference (RR = 1.60, 95% CI: 1.10, 2.32; RD = 0.10, 95% CI: 0.10, -0.04, 0.23).

3.2.2 Combination varenicline

Treatment-naïve population

- Varenicline in combination with NRT patch was shown to be superior to varenicline alone in terms of efficacy, but the results were no longer significant after excluding one RCT identified to be different in study design (pre-cessation treatment with patch) and participant characteristics (more females than males). There were no statistically significant differences between varenicline plus NRT patch and varenicline alone in terms of nausea, insomnia, abnormal dreams, or headache.
- There were no statistically significant differences between varenicline plus bupropion compared to varenicline alone in terms of efficacy. While a significantly higher proportion of patients in the varenicline plus bupropion arm experienced any adverse events and psychiatric adverse events compared with patients in the varenicline alone arm, there were no statistically significant differences in serious adverse events and discontinuation due to adverse events.

Comparison	Included studies	Summary of evidence
Treatment-naïve population		
Varenicline + NRT patch vs varenicline alone	• Chang (2015)[2]	• <u>Efficacy</u>: Statistically significant[3] based on OR (in favour of varenicline+NRT patch). • <u>Safety</u>: Not statistically significant based on OR (nausea, insomnia, abnormal dreams, headache).
Varenicline + bupropion vs varenicline alone	• Howes (2020)[1]	• <u>Efficacy</u>: Not statistically significant based on RR. • <u>Safety</u>: Statistically significant based on RR (any AEs, psychiatric AEs; higher in varenicline+bupropion); Not statistically significant based on RR (SAEs, discontinuation due to AEs).

Abbreviations: AEs = adverse events; NRT = nicotine replacement therapy; OR = odds ratio; RR = risk ratio, RD = risk difference; SAEs = serious adverse events.
Notes:
1 Cochrane Review.
2 Non-Cochrane systematic review.
3 The results were no longer significant after excluding one RCT identified to be different in study design (pre-cessation treatment with patch) and participant characteristics (more females than males).

3.2.3 Combination bupropion

Treatment-naïve population

- There were no statistically significant differences between bupropion in combination with NRT compared to NRT alone (either as patch, lozenge, or choice of NRT) in terms of efficacy. While a significantly higher proportion of patients in the bupropion plus NRT arm experienced any adverse events compared with patients in the NRT alone arm, there were no statistically significant differences in serious adverse events and discontinuation due to adverse events.

Comparison	Included studies	Summary of evidence
Treatment-naïve population		
Bupropion + NRT[1] vs NRT monotherapy	• Howes (2020)[2]	• <u>Efficacy</u>: Not statistically significant based on RR. • <u>Safety</u>: Statistically significant based on RR (any AEs; higher in bupropion+NRT); Not statistically significant based on RR (SAEs, discontinuation due to AEs).

Abbreviations: AEs = adverse events; NRT = nicotine replacement therapy; RR = risk ratio; SAEs = serious adverse events.
Notes:
1 NRT administered either as patch, lozenge, or choice of NRT.
2 Cochrane Review.

Treatment-experienced population

• There were no statistically significant differences between bupropion in combination with NRT (either as gum or inhaler) compared to placebo as a relapse prevention treatment in abstainers. The adverse events reported were consistent with those expected of bupropion and NRT.

Comparison	Included studies	Summary of evidence
Treatment-experienced population (relapse prevention treatment in abstainers)		
Bupropion + NRT[1] vs placebo	• Livingstone-Banks (2019)[2]	• <u>Efficacy</u>: Not statistically significant based on RR. • <u>Safety</u>: AEs reported were consistent with those expected of bupropion and NRT.

Abbreviations: AEs = adverse events; NRT = nicotine replacement therapy; RR = risk ratio.
Notes:
1 NRT administered either as gum or inhaler.
2 Cochrane Review.

3.3 NRT dose, dosage form and length of therapy

Examine the efficacy and safety of NRT with respect to dose, dosage form, length of therapy and combination therapy

3.3.1 NRT dose

• Higher strength NRT patches (21 mg/24-hour) were shown to be superior to lower strength patches (14 mg/24-hour) in terms of efficacy based on trials that primarily involved participants who smoked 20 or more cigarettes a day. There were no statistically significant differences in smoking cessation rates for the other comparisons (25 mg/16-hour versus 15 mg/16-hour patches; 42/44 mg/24-hour versus 21/22 mg/24-hour patches). In Lindson et al. (2019), studies comparing 42 mg/24-hour versus 21 mg/24-hour and 44 mg/24-hour versus 22 mg/24-hour patches were pooled. For safety, there were no statistically significant differences in the key adverse events between higher strength and lower strength NRT patches for all comparisons except for treatment withdrawals comparing the 42/44 mg with 21/22 mg (24-hour) patches, with a significantly higher treatment withdrawal rate observed in patients treated with 42/44 mg (24-hour) patches.

• Higher strength NRT gum (4 mg) was shown to be superior to lower strength gum (2 mg) in terms of efficacy based on the pooled results of high-dependency and low-dependency smokers. However, the results of the subgroup analysis suggest that only smokers who are highly dependent may benefit from the higher strength NRT gum. There were no

statistically significant differences in palpitations and treatment withdrawals between the two treatment arms.

Comparison	Included studies	Summary of evidence
Higher strength NRT patch[1] vs lower strength NRT patch	• Lindson (2019)[3]	• <u>Efficacy</u>: Statistically significant based on RR (in favour of higher strength, 21 mg/24-hour versus 14 mg/24-hour); Not statistically significant based on RR (other comparisons). • <u>Safety</u>: Statistically significant based on RR (treatment withdrawals; higher in 42/44 mg/24-hour patch); Not statistically significant based on RR (AEs incl. treatment withdrawals for other comparisons).
Higher strength NRT gum[2] vs lower strength NRT gum	• Lindson (2019)[3]	• <u>Efficacy</u>: Statistically significant[2] based on RR (in favour of higher strength). • <u>Safety</u>: Not statistically significant based on RR (palpitations, treatment withdrawals).

Abbreviations: AEs = adverse events; NRT = nicotine replacement therapy; RR = risk ratio.
Notes:
1 Comparisons include 21 mg/24-hour versus 14 mg/24-hour patches, 25 mg/16-hour versus 15 mg/16-hour patches, and 42/44 mg/24-hour versus 21/22 mg/24-hour patches. Studies comparing 42 mg/24-hour versus 21 mg/24-hour and 44 mg/24-hour versus 22 mg/24-hour patches were pooled.
2 Comparisons include 4 mg versus 2 mg gum. Based on the pooled results of high-dependency and low-dependency smokers. The results of the subgroup analysis suggest that only smokers who are highly dependent may benefit from the higher strength NRT gum.
3. Cochrane Review.

3.3.2 Length of therapy

- There were no statistically significant differences between longer duration NRT and shorter duration NRT in terms of efficacy and safety (serious adverse events and treatment withdrawals). For this comparison, NRT was administered either as monotherapy (patch or gum) or combination therapy. Of note, the CEASE (1999) study compared 28 weeks with 12 weeks of NRT patches, with two patch doses (25 mg and 15 mg) examined in each duration showed no statistically significant differences consistent with the other studies identified.
- For other variations in NRT use (24-hour versus 16-hour patches, continue versus stop patch use on relapse, and 22 weeks of a combination of 35 mg patches and fast-acting NRT versus 10 weeks of 21 mg patches), there were no statistically significant differences in smoking cessation rates, serious adverse events, treatment withdrawals and cardiac events in all comparisons.

Comparison	Included studies	Summary of evidence
Longer duration NRT[1] vs shorter duration NRT	• Lindson (2019)[3] • Ellerbeck (2018)[4]	• <u>Efficacy</u>: Not statistically significant based on RR. • <u>Safety</u>: Not statistically significant based on RR (overall SAEs, treatment withdrawals, and midsternal pressure).
Other variations in NRT use[2] vs other variations in NRT use	• Lindson (2019)[3]	• <u>Efficacy</u>: Not statistically significant based on RR. • <u>Safety</u>: Not statistically significant based on RR (cardiac AEs, SAEs, treatment withdrawals).

Abbreviations: AEs = adverse events; NRT = nicotine replacement therapy; RR = risk ratio; SAEs = serious adverse events

Notes:

1 Comparisons include various durations of longer duration NRT versus shorter duration NRT (either as patch, gum, or combination therapy).

2 Comparisons include 24-hour versus 16-hour patches, continue versus stop patch use on relapse, and 22 weeks of a combination of 35 mg patches and fast-acting NRT (gum or inhaler) versus 10 weeks of 21 mg patches.

3 Cochrane Review.

4 Supplemental evidence (RCT).

3.3.3 Dosing schedule

- There were no statistically significant differences between abrupt withdrawal of NRT patches compared to tapering patch dose in terms of efficacy and safety (treatment withdrawal). This is consistent with previous PBAC considerations, whereby gradual tapering compared with abrupt withdrawal was expected to result in minimal changes in clinical outcomes.

- There were no statistically significant differences between fixed dosing schedules for fast-acting NRT compared to ad lib dosing schedule in terms of efficacy and safety (serious adverse events and treatment withdrawals) for all comparisons (gum, nasal spray, and pooled analysis).

- Preloading use of NRT (prior to smoking cessation) was shown to be superior to standard use of NRT (commencing at the time of smoking cessation) in terms of efficacy. However, the results were only statistically significant in the NRT patches subgroup and not in the NRT gum or NRT patch in combination with gum subgroups. For safety, there was a significantly higher proportion of patients in the preloading arm experiencing palpitations compared with patients in the standard use arm, however, there were no statistically significant differences in cardiac adverse events, cardiac serious adverse events, overall serious adverse events, and treatment withdrawals.

- Reduction in cigarettes per day ('cutting down to quit') with pharmacotherapy was shown to be superior to reduction alone in terms of efficacy in the fast-acting NRT subgroup, noting that there were no statistically significant differences between the two treatment arms in either combination NRT or NRT patches subgroups. There were no statistically significant differences in pre-quit adverse events and pre-quit serious adverse events between cutting down to quit with pharmacotherapy and cutting down alone.

Comparison	Included studies	Summary of evidence
Abrupt withdrawal of NRT patch vs gradual tapering of NRT patch	• Lindson (2019)[4]	• <u>Efficacy</u>: Not statistically significant based on RR. • <u>Safety</u>: Not statistically significant based on RR (treatment withdrawals).
Fixed dosing schedule[1] vs ad lib dosing schedule	• Lindson (2019)[4]	• <u>Efficacy</u>: Not statistically significant based on RR. • <u>Safety</u>: Not statistically significant based on RR (SAEs, treatment withdrawals).
Preloading use of NRT[2] vs standard use of NRT	• Lindson (2019)[4] • Dedert (2018)[5]	• <u>Efficacy</u>: Statistically significant based on RR and RD (in favour of preloading use for NRT patch); not statistically significant based on RR (other comparisons). • <u>Safety</u>: Statistically significant based on RR (palpitations; higher in preloading use); Not statistically significant based on RR (cardiac AEs, cardiac SAEs, treatment withdrawals), and RD (overall SAEs).
Reduction with pharmacotherapy (pre-quit)[3] vs reduction alone	• Lindson (2019b)[4]	• <u>Efficacy</u>: Statistically significant based on RR (in favour of reduction with pharmacotherapy for fast-acting NRT); not statistically significant based on RR (other comparisons). • <u>Safety</u>: Not statistically significant based on RR (pre-quit SAEs); Inconclusive for pre-quit AEs (statistically significant in one RCT but not statistically significant in another RCT).

Abbreviations: AEs = adverse events; NRT = nicotine replacement therapy; RR = risk ratio, RD = risk difference; SAEs = serious adverse events.

Notes:

1 Comparisons include gum, nasal spray, and pooled analysis.

2 Comparisons include preloading use (prior to smoking cessation) versus standard use (commencing at the time of smoking cessation) of NRT patches, NRT gum or NRT patch in combination with gum. Pooled analysis of efficacy was statistically significant, in favour of preloading use.

3 Comparisons include NRT patches, fast-acting NRT, and combination NRT. Reduction in cigarettes per day refers to 'cutting down to quit'.

4 Cochrane Review.

5 Supplemental evidence (RCT).

3.3.4 Non-PBS-listed NRT dosage forms

Inhalator

• There were no statistically significant differences between NRT inhalators and placebo in terms of efficacy based on the results of the updated re-analysis after including the study identified in the supplemental literature search (Oncken et al. 2019), noting that the results were statistically significant in Hartmann-Boyce et al. (2018). For safety, there were no statistically significant difference in adverse events between the two treatment arms (risk ratio), noting that the results were statistically significant based on risk difference.

• There were no statistically significant differences between NRT inhalators compared to patches in terms of efficacy. For safety, there were no serious adverse events reported in either treatment arm.

Comparison	Included studies	Summary of evidence
NRT inhalator vs placebo	• Hartmann-Boyce (2018)[1] • Oncken (2019)[2]	• Efficacy: Not statistically significant based on RR and RD. • Safety: Not statistically significant[3] based on RR and RD (any AEs).
NRT inhalator vs NRT patch	• Lindson (2019)[1]	• Efficacy: Not statistically significant based on RR. • Safety: No SAEs reported in either arm.

Abbreviations: AEs = adverse events; NRT = nicotine replacement therapy; RR = risk ratio, RD = risk difference; SAEs = serious adverse events.
Notes:
1 Cochrane Review.
2 Supplemental evidence (RCT).
3 Not statistically significant based on risk ratio but significant based on risk difference (RR = 16.28, 95%CI: 0.96, 276.65; RD = 0.11, 95%CI: 0.04, 0.19).

Nasal spray

- NRT nasal spray was shown to be superior to placebo in terms of efficacy. In terms of safety, the results of the meta-analysis comprising three RCTs demonstrated a significantly higher incidence of palpitations/chest pains adverse events in the nasal spray arm compared to placebo.
- There were no statistically significant differences between NRT nasal spray and NRT patches in terms of efficacy. Among the studies comparing nasal spray with patches, Lerman et al. (2004) reported no serious adverse events in either treatment arms, while Croghan et al. (2003) showed a significantly higher rate of treatment withdrawals in the nasal spray treatment arm.

Comparison	Included studies	Summary of evidence
NRT nasal spray vs placebo	• Hartmann-Boyce (2018)[1]	• Efficacy: Statistically significant based on RR (in favour of NRT nasal spray). • Safety: Statistically significant based on RR (palpitations/chest pains; higher in NRT nasal spray).
NRT nasal spray vs NRT patch	• Lindson (2019)[1]	• Efficacy: Not statistically significant based on RR. • Safety: Statistically significant based on RR (treatment withdrawals; higher in NRT nasal spray); No SAEs reported in either arm.

Abbreviations: NRT = nicotine replacement therapy; RR = risk ratio; SAEs = adverse events.
Notes:
1 Cochrane Review.

Oral spray

- NRT oral spray was shown to be superior to placebo in terms of efficacy, noting that the results of the updated re-analysis were not statistically significant based on risk difference (absolute effect). A significantly higher proportion of patients in the oral spray arm experienced any adverse events and discontinuation due to adverse events compared with patients in the placebo arm. No patients in either arm experienced treatment-related serious adverse events.

Comparison	Included studies	Summary of evidence
NRT oral spray vs placebo	• Hartmann-Boyce (2018)[1] • Nides (2020)[2]	• <u>Efficacy</u>: Statistically significant based on RR (in favour of NRT oral spray), but not statistically significant for RD[3]. • <u>Safety</u>: Statistically significant based on RR and RD (any AEs, discontinuation due to AEs; higher in NRT oral spray); No SAEs reported in either arm.

Abbreviations: AEs = adverse events; NRT = nicotine replacement therapy; RR = risk ratio, RD = risk difference; SAEs = serious adverse events.
Notes:
1 Cochrane Review.
2 Supplemental evidence (RCT).
3 Statistically significant based on risk ratio but not significant based on risk difference (RR = 2.63, 95% CI: 1.54, 4.50; RD = 0.05, 95%CI: -0.02, 0.12).

Inhalator and patch

• There were no statistically significant differences between NRT inhalator + patch and placebo in terms of efficacy based on long-term smoking cessation rates. The one study identified by Hartmann-Boyce et al. (2018) did not assess the comparative safety of NRT inhalator + patch versus placebo.

Comparison	Included studies	Summary of evidence
NRT inhalator and patch vs placebo	• Hartmann-Boyce (2018)[1]	• <u>Efficacy</u>: Not statistically significant based on RR. • <u>Safety</u>: Safety outcomes were not assessed by the study.

Abbreviations: NRT = nicotine replacement therapy; RR = risk ratio.
Notes:
1 Cochrane Review.

3.4 Behavioural interventions in combination with pharmacotherapies

Examine the importance of comprehensive support and counselling in combination with pharmacotherapies

• The evidence presented from six identified Cochrane Reviews comparing the efficacy of specific behavioural support with minimal or no behavioural interventions (both in combination with pharmacotherapies) was inconclusive. The type of behavioural interventions examined were different for each review.

• The results of smoking cessation rates from three Cochrane Reviews (Lancaster 2017, Carson-Chahhoud 2019, and Matkin 2019) were statistically significantly different, in favour of behavioural intervention when used in combination with pharmacotherapies. The behavioural interventions examined were proactive telephone counselling, more intensive face-to-face behavioural interventions delivered by community pharmacy personnel, and individual face-to-face counselling by a trained smoking cessation counsellor. The primary evidence previously considered by the PBAC for bupropion, varenicline, and NRT patches included the provision of individual counselling sessions in addition to pharmacotherapy.

• In contrast, two of the Cochrane Reviews (Stead 2017, Livingstone-Banks 2019b) that examined group therapy and print-based self-help materials respectively demonstrated no statistically significant difference in smoking cessation rates between the two

treatment arms, noting that the results numerically favoured the behavioural intervention in combination with pharmacotherapy treatment arm.

- In Hartmann-Boyce et al. (2019), comparing more intensive with less intensive behavioural therapy, a statistically significant improvement in smoking cessation rates was observed in patients receiving more intensive behavioural intervention when used in combination with NRT or bupropion. There were no statistically significant differences in smoking cessation rates between the more intensive and the less intensive arms when used in combination with varenicline or NRT plus bupropion, which was likely due to the smaller number of studies leading to lower precision rather than a true difference in effect. The results of the overall estimated pooled risk ratio irrespective of the type of pharmacotherapy (PBS-listed and non-PBS-listed) were statistically significantly different, in favour of the more intensive behavioural intervention.

3.5 Use in populations with specific needs

The evidence reviewed focused on populations in which the clinical guideline recommendations differed from the general population. ToR 1 presents the review of clinical guidelines and includes Aboriginal and Torres Strait Islander people and incarcerated persons amongst other populations; however, the guidelines did not recommend any differential use of smoking cessation therapies or indicate any differential effect of these therapies in any populations other than pregnancy and adolescents. This analysis excluded prescribing contraindications and precautions, as they are not typically handled via a PBS restriction.

Examine the evidence of efficacy and safety of smoking cessation medicines during pregnancy and for adolescents

3.5.1 Pregnancy and lactation

- NRT was shown to be superior to placebo/control in terms of efficacy based on self-reported abstinence from smoking at the latest time point in pregnancy (biochemically validated where available), noting the results were statistically significant in the long-acting NRT subgroup but not the fast-acting NRT subgroup. In terms of safety, there were no statistically significant differences in rates of preterm births, neonatal intensive care unit admissions, neonatal deaths, congenital abnormalities, caesarean birth, mean birthweight, and risk of miscarriage/spontaneous abortion between the two treatment arms.
- There were no statistically significant differences between bupropion and placebo in terms of efficacy based on self-reported abstinence from smoking at the latest time point in pregnancy (biochemically validated where available), noting the relatively small sample size of the individual studies. It was noted that women across all studies reported known adverse effects of bupropion (i.e., vomiting, headache, difficulty sleeping).

Comparison	Included studies	Summary of evidence
NRT vs placebo/control	• Claire (2020)[1]	• <u>Efficacy</u>: Statistically significant[2,3] based on RR (in favour of NRT). • <u>Safety</u>: Not statistically significant based on RR (preterm births, neonatal intensive care unit admissions, neonatal deaths, congenital abnormalities, caesarean birth, mean birthweight, risk of miscarriage/spontaneous abortion).
Bupropion vs placebo	• Claire (2020)[1]	• <u>Efficacy</u>: Not statistically significant[3] based on RR. • <u>Safety:</u> Not statistically significant (mean birthweight, mean length of infants and systolic of diastolic blood pressure at the end of pregnancy)[4].

Abbreviations: NRT = nicotine replacement therapy; RR = risk ratio.
Notes:
1 Cochrane Review.
2 Statistically significant in overall pooled analysis (RR = 1.37, 95%CI: 1.08, 1.74). Statistically significant in the long-acting NRT subgroup (RR = 1.53, 95%CI: 1.16, 2.01) but not the fast-acting NRT subgroup (RR = 0.91, 95%CI: 0.55, 1.51).
3 Based on self-reported abstinence from smoking at the latest time point in pregnancy (biochemically validated where available).
4 Qualitative synthesis.

3.5.2 Adolescents

• Studies which assessed the use of pharmacotherapy for smoking cessation in adolescents may be underpowered given the small number of individuals in both the intervention and control groups who achieved smoking cessation at any point during follow-up. As such, the results from these studies should be interpreted with caution.

• There were no statistically significant differences between NRT (either as patch, gum, or nasal spray) and placebo in terms of efficacy based on smoking cessation rates (short-term and long-term). For safety, the studies reported a significantly higher incidence of adverse events in the NRT arm compared to placebo arm, specifically sore throat, hiccups, erythema, pruritus, shoulder/arm pain, headache, cough, abnormal dreams, and muscle pain.

• There were no statistically significant differences between bupropion and placebo in terms of long-term efficacy based on the one study identified by Fanshawe et al. (2017). However, bupropion was shown to significantly improve smoking cessation rates compared with placebo based on the meta-analysis conducted by Myung et al. (2019), noting that the two additional studies included in the meta-analysis measured smoking cessation outcomes at three months, had a relatively small sample size and wide confidence intervals. For safety, there were no significant differences between bupropion and placebo (i.e., headache, irritability, insomnia), except for dream disturbances which was significantly higher in the bupropion arm.

• There were no statistically significant differences between bupropion plus NRT patch and placebo plus NRT patch in terms of efficacy based on long-term smoking cessation rates. For safety, none of the 47 self-reported adverse events in the study (nausea being the most common) were classified as severe; no statistical comparison was conducted by the authors of the study.

Comparison	Included studies	Summary of evidence
NRT[1] vs placebo	• Fanshawe (2017)[2] • Myung (2019)[3] • Selph (2020)[3]	• Efficacy: Not statistically significant[4] based on RR. • Safety: Statistically significant (sore throat, hiccups, erythema, pruritus, shoulder/arm pain, headache, cough, abnormal dreams, and muscle pain; higher in NRT)[5].
Bupropion vs placebo	• Fanshawe (2017)[2] • Myung (2019)[3] • Selph (2020)[3]	• Efficacy: Not statistically significant[6] based on RR. • Safety: Statistically significant (dream disturbances; higher in bupropion); Not statistically significant (headache, irritability, insomnia)[5].
Bupropion+ NRT patch vs placebo + NRT patch	• Fanshawe (2017)[2]	• Efficacy: Not statistically significant based on RR. • Safety: No statistical comparison was conducted by the authors.

Abbreviations: NRT = nicotine replacement therapy; RR = risk ratio.
Notes:
1 NRT administered either as patch, gum, or nasal spray.
2 Cochrane Review.
3 Non-Cochrane systematic review.
4 Based on short-term and long-term smoking cessation rates.
5 Qualitative synthesis.
6 Based on long-term smoking cessation rates. In Myung et al. (2019), the results were statistically significant based on a meta-analysis which included two additional studies, noting these studies measured smoking cessation outcomes at three months, had a relatively small sample size and wide confidence intervals.

3.6 Stakeholder views (forum and public consultations)

Clinicians indicated that they routinely prescribe combination NRT.

Stakeholders considered that the effectiveness of PBS-listed smoking cessation medicines could be improved by allowing:

- Combination therapy;
- Longer durations of NRT;
- Multiple courses per year; and
- Higher doses (increased quantities) of NRT.

Stakeholders also considered that smoking cessation medicines combined with behavioural intervention is the most effective way to quit.

Stakeholders identified common causes of unsuccessful quit attempts as:

- under dosing (dose and/or duration) of NRT
- insufficient management, follow-up, and support
- access issues, especially for people in rural and remote areas

Stakeholders noted several issues with study populations, including:

- Priority populations (such as people with mental illness and pregnant women) are usually excluded from studies, which may bias results in favour of the smoking cessation medicine.
- Study participants may not represent the broader community of smokers in terms of health literacy and willingness to engage in treatment, and the monitoring and follow-up built into the trial may serve as motivation.
- Health benefits are not usually a primary or secondary outcome that is measured in clinical studies, and studies focus on quit attempts.

- The time frame for study follow-up does not allow long-term monitoring of abstinence or subsequent relapse treatment and does not allow long-term health benefits (such as cardiovascular benefits) to be captured.

ToR 4: Cost-effectiveness review of specified combinations of smoking cessation medicines and estimates for the PBS

Subject to the findings of terms of reference 1, 2 and 3, review the cost-effectiveness of medicines for smoking cessation

In June 2021, the Economics Sub-Committee (ESC) considered the PMR of medicines for smoking cessation report and advised that a cost-effectiveness analysis of combination NRT versus NRT monotherapy and combination varenicline and NRT versus varenicline monotherapy should be progressed under ToR 4 of the Review.

The Centre for Health Economics, Monash University was contracted to conduct a cost-effectiveness review (CER) of specified combinations of medicines for smoking cessation and estimates for the PBS.

The economic analysis presented in the CER considers the relative cost-effectiveness of the following comparisons of medicines for smoking cessation:

1. varenicline monotherapy (VAR) versus NRT monotherapy (NRT)
2. Combination varenicline and NRT (VAR+NRT) versus VAR
3. VAR+NRT versus NRT
4. Combination NRT (NRT+NRT) versus VAR
5. NRT+NRT versus NRT
6. VAR+NRT and NRT+NRT versus VAR+NRT

And thus, provided evidence on the cost-effectiveness of the potential PBS listing of the following scenarios:

(i) VAR+NRT only
(ii) NRT+NRT only
(iii) both VAR+NRT and NRT+NRT

The research also provided estimates of the likely financial implications to the PBS of such listings.

4.1 Clinical evidence

The CER relied on the clinical evidence summarised in the ToR 3 report, as well as a recently published trial comparing VAR+NRT to VAR (6). The results of this recent RCT (Baker et al. 2021) were published after the ToR 3 report was completed. The RCT included four arms, VAR (12 weeks), VAR (24 weeks), VAR+NRT patch (12 weeks) and VAR+NRT patch (24 weeks). The continuous abstinence rate at 23 weeks of those receiving VAR monotherapy and VAR+NRT patch (combining the shorter and extended use arms) was 21.9% and 22.2% respectively. The study also included a longer follow-up and found the continuous abstinence rate at 52 weeks to be 16.1% and 16.6% respectively. The study found no significant difference in the head-to-head effectiveness of combination use (or extended use) compared to 12 weeks of VAR monotherapy.

To provide consistent evidence for the economic evaluation across the treatment options considered, this evidence was synthesised using a NMA. This differed to the approach taken in the ToR 3 report, which focused on meta-analysis of head-to-head evidence between any two of the cessation treatments. The NMA has the added advantage of making the most efficient use of the evidence available through also considering indirect comparisons. The NMA comprised of 53 RCTs with results at week 24 and 80 RCTs with results at week 52 (Refer to Section 3.4 'Transition probabilities and extrapolation' of the ToR 4 report for further detail).

4.2 Economic evaluation

The costs, health outcomes and incremental cost-effectiveness ratios (ICERs) for each of the stated comparisons, with a discount rate of 5%, are presented in Table 1 below. The first reported comparison compared the two major usual care options currently available, VAR versus NRT as the first line therapy, which resulted in an ICER between \$55,000 to < \$75,000 per quality-adjusted life-year (QALY). The estimated ICERs for VAR+NRT versus these usual care comparators, VAR and NRT, were within the range of \$35,000 to < \$45,000; whilst the estimated ICERs for NRT+NRT versus VAR and NRT were within the range of \$15,000 to < \$25,000 and \$25,000 to < \$35,000 respectively. The scenario of listing both VAR+NRT and NRT+NRT compared to listing VAR+NRT alone was found to be both costlier and less effective (i.e., was dominated).

Table 1: Main cost-effectiveness analysis results (5% discount rate)

Comparison	Costs ($AU)			Health outcomes (QALYs)			ICER range ($ per QALY)
	Proposed treatment	Comparator treatment	Diff.	Proposed treatment	Comparator treatment	Diff.	
(VAR) vs (NRT) [a]							
(VAR+NRT) [b] vs (VAR)							
(VAR+NRT) [b] vs (NRT)							
(NRT+NRT) [b] vs (VAR)							
(NRT+NRT) [b] vs (NRT)							
(VAR+NRT & NRT+NRT) [b] vs (VAR+NRT) [b]							

[a] This only considered the use of NRT versus VAR on the first attempt. The assumed use of NRT and VAR for subsequent attempts was assumed to be the same in both cases.

[b] Assumptions were also made about how the listing of these new combinations would also impact on the use of products in subsequent quit attempts. These results were produced by simulating 600,000 patients through each possible scenario for 50 years. 600,000 patients were used to minimise the Monte Carlo error.

4.3 Predicted use and budget impact analysis

Table 2 below presents the estimated financial implications to the PBS/Repatriation Pharmaceutical Benefits Scheme (RPBS), MBS, and the health system combined in each financial year to 2026-2027 for the three listing scenarios: VAR+NRT only (Scenario 1), NRT+NRT only (Scenario 2) and both VAR+NRT and NRT+NRT (Scenario 3). Under the base

case assumptions, the incremental cost to the PBS for the first five-years is approximately $60 million to < $70 million for Scenario's 1 and 2 and $90 million to < $100 million for Scenario 3. The proposed additional listings first increase costs given the substitution to more expensive therapy, but the more effective therapies are then assumed to reduce the need for future assisted quit attempts. Also, it is assumed that the substitution to the newly listed therapies will increase over time as more clinicians change their standard of care.

Table 2: Estimated incremental net cost to the PBS/RPBS (less co-payment) and MBS under the proposed listing scenarios relative to the current PBS restrictions

	2022-2023	2023-2024	2024-2025	2025-2026	2026-2027
Scenario 1 (VAR+NRT listed on the PBS)					
PBS/RPBS net cost (less co-pay)					
VAR					
NRT					
BUP					
MBS net cost					
Health budget net cost					
Scenario 2 (NRT+NRT listed on the PBS)					
PBS/RPBS net cost (less co-pay)					
VAR					
NRT					
BUP					
MBS net cost					
Health budget net cost					
Scenario 3 (both VAR+NRT and NRT+NRT listed on the PBS)					
PBS/RPBS net cost (less co-pay)					
VAR					
NRT					
BUP					
MBS net cost					
Health budget net cost					

A significant proportion of these additional costs are likely to come from those currently making attempts using OTC products or those who are already using combination products by supplementing their PBS prescription with OTC products. Further subsidising quit attempts may encourage adherence which may also increase successful quitting. These financial estimates rely heavily on the extent of the substitution away from existing products and whether these existing products are currently accessed OTC or through the PBS and there remains significant uncertainty regarding the rates of substitution we may see in practice. Assuming higher rates of substitution, such that combination therapy replaces most monotherapy on the PBS or where twice as many patients switch from non-PBS to PBS-therapy, increases these estimates by 20% to 75%. There is also a risk that the financial implications may be considerably greater than those estimated above should the proposed listing of combination therapy encourage patients to make additional assisted quit attempts.

These estimates also ignore the likely financial implications that will arise due to the current shortage of varenicline. A sensitivity analysis accounting for this market shock found that the impact on the incremental costs depends on the extent that other PBS-listed therapies (NRT and bupropion) would substitute for VAR when unavailable.

4.4 Stakeholder views (forum and public consultations)

Stakeholders considered that optimising the use of smoking cessation therapies on the PBS (such as allowing combination therapy or allowing dosage or length of treatment to be

tailored to the individual) would lead to more successful quit attempts and therefore cost-effectiveness would be improved.

Stakeholders noted the significant quality of life and financial burden the health consequences of smoking have on individuals and on society. Stakeholders considered that any additional costs to the PBS for optimising smoking cessation therapy would be outweighed by savings in treating smoking related diseases, such as hypertension.

Some stakeholders recommended that a CER should include the addition of the nicotine mouth spray and nicotine inhalator to the PBS.

Review 'options'

The following 'options' were raised by the reference group for the PMR of medicines for smoking cessation, in considering the available evidence. The Drug Utilisation Sub-Committee (DUSC) and the ESC will also provide advice on the following review options. These options are provided to the PBAC to assist in their consideration and formulation of recommendations and advice to government.

Any alteration to the restrictions surrounding the Pharmaceutical Benefits Scheme listing of medicines for smoking cessation would need to consider any impact on the cost-effectiveness of these medicines and the net cost to the PBS.

5.1 Option 1

Option 1a

- Allow an additional 12 weeks of PBS-subsidised NRT therapy in a 12-month period for non-Indigenous patients, for re-treatment of patients who had an unsuccessful quit attempt.

AND

Option 1b

- Allow an additional 12 weeks of PBS-subsidised NRT therapy in a 12-month period for non-Indigenous patients, who have ceased smoking during the initial 12 weeks of therapy to prevent relapse.

Note: Aboriginal and Torres Strait Islander persons already have access to 24 weeks of PBS-subsidised NRT in a 12-month period.

Rationale

- Stakeholder feedback supported extending the length of NRT therapy available on the PBS to increase the treatment options available for prescribers and consumers.
- The reference group noted that there was a lack of evidence from ToR 3 to support longer durations of treatment with NRT however, it supported removing barriers to people accessing smoking cessation products and greater flexibility for clinicians by allowing longer durations or multiple attempts at stopping within the same year, as this is consistent with public health messaging.
- The utilisation review of PBS medicines for smoking cessation (ToR 2) found only 12% of consumers prescribed NRT fill prescriptions for the full 12 weeks duration of therapy, suggesting that uptake (via the PBS) of longer durations of therapy will be low. Additionally, there was no significant difference in the median duration of NRT use between the general population and the Aboriginal and Torres Strait Islander population who currently have access to 24 weeks of PBS-subsidised NRT.

Background and evidence considered by the reference group

The current PBS restrictions state that "*Patient must not receive more than 12 weeks (or 24 weeks for Aboriginal and Torres Strait Islander people) of PBS-subsidised nicotine replacement therapy per 12-month period.*" A course of NRT refers to 12 weeks of therapy available on the PBS. This may be prescribed as one original script and 2 repeats. Consumers do not need to

return to the prescriber to complete the 12 weeks of therapy. The PBS does not allow for an increase in quantity or repeats.

Restrictions for Aboriginal and Torres Strait Islander persons currently allow for 24 weeks of therapy in a 12-month period. The wording of the restriction allows Aboriginal and Torres Strait Islander persons to access the additional course of NRT beyond 12 weeks, or to use it for a subsequent quit attempt within the 12-month period. To gain access to the additional course of therapy consumers would be required to return to the prescriber to access additional prescriptions. However, for consumers accessing NRT through the s100 Remote Area Access Scheme (RAAS) a prescription is not required.

The Review Report for ToR 3 found the following in respect to treatment experienced consumers:

- NRT has not previously been considered by the PBAC for treatment-experienced patients.
- There were no statistically significant differences between NRT (either as gum or inhaler) and placebo in terms of efficacy as a relapse prevention treatment in abstainers. The adverse events reported were consistent with those expected of NRT.
- The results of Gourlay et al. (1995), based on continuous abstinence rate, demonstrated no statistically significant difference between NRT patches and placebo in non-abstainers as retreatment at 6 months. However, there was a statistically significant improvement in smoking cessation rates using NRT patches based on 28-day point prevalence abstinence (RR: 2.49; 95% CI: 1.11, 5.57) at this point in the study by Gourlay et al. (1995) only. In terms of safety, there were no statistically significant differences between the two treatment arms for palpitations, tachycardia, or chest pains.

The Review Report for ToR 3 also found the following with respect to length of treatment for NRT:

- There were no statistically significant differences between longer duration NRT and shorter duration NRT in terms of efficacy and safety (serious adverse events and treatment withdrawals). For this comparison, NRT was administered either as monotherapy (patch or gum) or combination therapy.
- For other variations in NRT use (24-hour versus 16-hour patches, continue versus stop patch use on relapse, and 22 weeks of a combination of 35 mg patches and fast-acting NRT versus 10 weeks of 21 mg patches), there were no statistically significant differences in smoking cessation rates, serious adverse events, treatment withdrawals and cardiac events in all comparisons.

5.2 Option 2

Option 2a

- Remove the requirement for nicotine patch, lozenge, or gum to be used as monotherapy to allow for combinations of NRT patch + short acting formulations to be used concomitantly on the PBS.

AND

Option 2b

- Remove the requirement for nicotine patch, to be used as monotherapy to allow for combinations of NRT patch formulations to be used on the PBS, to allow for double

patching (e.g., two 21 mg/24 hours patches daily, 21mg + 14mg/24 hour patches daily) as second line therapy under an authority required restriction. Alternatively, double patching could be achieved by allowing increased quantities to be approved via a phone or online authority.

Rationale 2a

- In the Review Report, combination NRT was shown to be superior to NRT monotherapy (patch or fast-acting - including gum and lozenge) in terms of efficacy. In terms of safety, there were no statistically significant differences in cardiac adverse events, serious adverse events, or withdrawals due to treatment.
- The use of two forms of NRT at the same time is consistent with all guidelines reviewed in ToR 1 and TGA-approved dosing of NRT.
- Stakeholders strongly supported allowing combination NRT use on the PBS.
- The reference group acknowledged that if the PBAC was of a mind to support combination therapy with NRT products listed on the PBS, it would need to consider the cost-effectiveness and net cost to government as part of any final recommendation.
- Based on the Cochrane Review by Hartmann-Boyce (2018) and one RCT (Chen 2020), combination NRT (patch + lozenge, patch + lozenge and gum) was shown to be superior to placebo in terms of efficacy. There were no statistically significant differences between NRT patch + lozenge and placebo in terms of any adverse events and serious adverse events.
- For the comparison of NRT patch + gum versus placebo, there were no statistically significant differences between the two treatment arms based on the meta-analysis of two studies conducted by Hartmann-Boyce et al. (2019), although the results numerically favoured NRT patch + gum. The non-significant result of NRT patch + gum was likely due to study design issues, such as small sample size, leading to insufficient power to detect a modest treatment effect with reasonable certainty.
- Based on one direct RCT (Chen 2020), combination NRT (patch + lozenge) was shown to be inferior to varenicline in terms of efficacy with no statistically significant differences in terms of safety. However, based on the results of the NMA by Cahill et al. (2013), there was no statistically significant difference in smoking cessation rates between combination NRT and varenicline, although the results numerically favoured varenicline. The results of the NMA should be interpreted with caution due to potential biases and uncertainties arising from heterogeneity and inconsistent outcomes between studies.[4]

Rationale 2b

- The reference group considered that high dose NRT was a useful treatment option for some patients who are highly nicotine dependent. However, they considered PBS restrictions should not allow higher doses (higher than 21mg/hr) first line and clinicians

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[4] The efficacy of combination NRT relative to varenicline was investigated further as part of the ToR 4 report. For further information refer to p.43 of 'ToR 4: Cost-effectiveness review of specified combinations of smoking cessation medicines and estimates for the Pharmaceutical Benefits Scheme.'

should first trial standard dose NRT to avoid unnecessary treatment withdrawal and wastage. The reference group supported allowing high dose NRT under the PBS with an authority required level of restriction or increased quantities via authority approval.

- The reference group also noted that higher doses of NRT can be achieved by allowing combination NRT to be subsidised under the PBS.
- Stakeholders considered that the effectiveness of PBS-listed smoking cessation medicines could be improved by allowing higher doses (i.e., increased quantities) of currently listed NRT patches.
- In the Cochrane Review by Lindson (2019), higher strength NRT patches (21 mg/24-hour) were shown to be superior to lower strength patches (14 mg/24-hour) in terms of efficacy. However, there were no statistically significant differences in smoking cessation rates reported for the other comparisons (25 mg/16-hour versus 15 mg/16-hour patches; 42/44 mg/24-hour versus 21/22 mg/24-hour patches). The majority of trials included in the Cochrane Review involved participants with a high level of dependence, who smoked 20 or more cigarettes a day.
- For the assessment of safety, there were no statistically significant differences in the key adverse event rates between higher strength and lower strength NRT patches, except for treatment withdrawals. The comparison between the 42/44 mg and 21/22 mg (24-hour) patches reported a significantly higher treatment withdrawal rate in patients treated with 42/44 mg (24-hour) patches.
- The allowable quantities for NRT patches in the current PBS restrictions do not account for 'double-patching' although several guidelines suggested that this may be useful for heavily dependent smokers.

Background

The current PBS restrictions for NRT state "*the treatment must be the sole PBS-subsidised therapy for this condition".*

Combinations of NRT for smoking cessation have not been previously considered by the PBAC. In March 2018, the PBAC noted that the latest clinical guidelines encouraged health professionals to consider recommending the use of combination NRT (e.g., NRT patch with NRT gum or lozenges).

5.3 Option 3

- Remove the requirement for varenicline to be used as monotherapy, to allow for use in combination with NRT on the PBS.

Rationale

- The Review Report found that varenicline in combination with NRT patch was shown to be superior to varenicline alone in terms of efficacy, but the results were no longer significant after excluding one RCT identified that had a different study design and participant characteristics. There were no statistically significant differences between varenicline plus NRT patch and varenicline alone in terms of nausea, insomnia, abnormal dreams, or headache.
- The reference group acknowledged that cost-effectiveness modelling for varenicline + NRT versus varenicline would be informative if the PBAC consider combination varenicline + NRT a clinically effective treatment.

- Two national guidelines (RACGP and Cancer Council Victoria) and one international guideline (Canada) recommended the use of varenicline in combination with NRT as an alternative to varenicline alone.
- There were no statistically significant differences between varenicline plus bupropion compared to varenicline alone in terms of efficacy. While a significantly higher proportion of patients in the varenicline plus bupropion arm experienced any adverse events and psychiatric adverse events compared with patients in the varenicline alone arm, there were no statistically significant differences in serious adverse events and discontinuation due to adverse events.

Background

The current PBS restrictions for varenicline state, *"the treatment must be the sole PBS-subsidised therapy for this condition".* The PBAC has not previously considered a submission for the listing of varenicline in combination with NRT of bupropion.

5.4 Option 4

- Recommend an education campaign targeting prescribers to raise awareness of the improved effectiveness of smoking cessation pharmacotherapies when provided in combination with comprehensive support and counselling and enable prescribers to support best practice in recommending or providing comprehensive support and counselling services.

Rationale

- The evidence considered in the Review Report found that smoking cessation rates improved when the following forms or counselling were used:
  - proactive telephone counselling,
  - more intensive face-to-face behavioural interventions delivered by community pharmacy personnel, and
  - individual face-to-face counselling by a trained smoking cessation counsellor.
- There was no difference in smoking cessation rates when using group therapy and print-based self-help materials.
- Hartmann-Boyce et al. (2019) compared more intensive forms of behavioural therapy with less intensive forms. The analysis found a statistically significant improvement in smoking cessation rates for more intensive pharmacotherapy, irrespective of the type of pharmacotherapy. For specific pharmacotherapies the results found:
  - A statistically significant improvement in smoking cessation rates in patients receiving more intensive behavioural intervention when used in combination with NRT or bupropion.
  - No statistically significant differences in smoking cessation rates between the more intensive and the less intensive arms when used in combination with varenicline or NRT plus bupropion, which was likely due to the smaller number of studies leading to lower precision rather than a true difference in effect.
- The findings from ToR 2 suggest the number of calls/contacts with Quitline were significantly less than the number of people dispensed smoking cessation medicines under the PBS. The reference group noted that consumers may receive counselling through other means, such as through a general practitioner (GP).

- The reference group considered that changes to the PBS restriction criteria for counselling would be difficult to enforce and would not improve counselling received by patients.

Background

PBS restrictions for smoking cessation therapy state that "*patient 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. Details of the support and counselling program must be documented in the patient's medical records at the time treatment is initiated.*"

The exception is the current PBS restrictions for Aboriginal and Torres Strait Islander people, which recommend comprehensive support and counselling, but do not require it for PBS subsidy.

5.5 Option 5

- Consider the PBS listing of nicotine inhaler* and/or nicotine mouth spray.

*Nicotine inhaler products do not include electronic cigarettes or e-liquids which were excluded from the PMR of medicines for smoking cessation.

Rationale

- Stakeholders felt that all forms of NRT should be subsidised under the PBS because various formulations may not be clinically appropriate for certain patients. This includes nicotine inhalers and mouth spray.
- The reference group acknowledged that the PBAC would require a sponsor or other entity to make a submission requesting the PBS listing of these products demonstrating efficacy, safety and cost-effectiveness before a recommendation can be made.
- The Review Report for ToR 3 found that:
  o There were no statistically significant differences between NRT inhalers compared to patches in terms of efficacy in Lindson (2019). A statistically significant difference was found between NRT inhalers and placebo in Hartmann-Boyce et al. (2018) however, no statistically significant differences were found based on the results of the updated re-analysis after including the study identified in the supplemental literature search (Oncken et al. 2019).
  o NRT oral spray was shown to be superior to placebo in terms of efficacy.

Background

The forms of NRT available on the PBS are:

- Nicotine patches (21mg/24hrs, 14mg/24hrs, 7mg/24hrs and 25mg/16hrs)
- Nicotine gum 2mg and 4mg
- Nicotine lozenge 2mg and 4mg

The PBAC has not previously considered a submission for either nicotine inhaler or nicotine spray formulations.

Other Advice the PBAC may wish to consider providing to Government

5.6 Option 6

- That the department follow-up with Queensland Quitline following its evaluation of the 'Intensive Quit Support Program' and to explore if there are other effective ways of providing access to government funded NRT in addition to the current PBS and section 100 arrangements.

Rationale

- The reference group noted evidence from the Review Report suggesting that the majority of NRT products are obtained OTC. The Review Report for ToR 2 found:
    - PBS use of NRT in 2019 represented 7% of all NRT use in Australia. In the financial year 2019/2020 NRT patches accounted for 94% of all NRT products subsidised under the PBS, while the majority of NRT products sold OTC were nicotine gums. However, nicotine gum and lozenge were only PBS-listed in February 2019 and therefore uptake of these forms of NRT may not have been fully realised
    - There were 257.4 million NRT smoking cessation aids sold OTC in 2019. The most commonly sold aid was NRT gum (194 million units in 2019), followed by NRT Lozenges (43.2 million units in 2019) and NRT patches.
- General patients are required to pay 3 co-payments for a 12-week course of NRT under the PBS, which amounts to $123.90, which may be a barrier to some patients. Further information on the costs of NRT products is provided in Table 2, p.12 of the Review Background report.
- Stakeholders considered that the cost of OTC NRT can be a significant barrier for many people, particularly those from populations with higher rates of smoking such as lower socioeconomic groups, Aboriginal and Torres Strait Islander people, and people with a mental illness. Stakeholders considered that financial cost was an important factor in unsuccessful quit attempts.
- The reference group did not recommend specific alternative arrangements (in addition to the current PBS arrangements) for the subsidised supply of NRT but recommended that the department follow-up with Queensland Quitline following its evaluation of the 'Intensive Quit Support Program' to explore if there are other ways of providing access to government funded NRT.

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Appendix A – Reference group members

Name	Nominated By	Capacity of Appointment
Professor Sanchia Aranda	Department of Health	Chair
Associate Professor Nicole Pratt	DUSC	Technical Expert
Professor Gillian Gould	Department of Health	Technical Expert
Professor Rashmi Sharma	Royal Australian College of General Practitioners	Technical Expert
Associate Professor Billingsley Kaambwa	Australian Health Economics Society	Technical Expert
Dr Angela Gowland	Therapeutic Goods Administration	Organisational Nominee
Associate Professor Richard Brightwell	Consumers Health Forum of Australia	Consumer Advocate
Yelitte Ho and Anonnya Chowdhury	Medicines Australia	Organisational Nominee