AUSTRALIAN PRODUCT INFORMATION – NICOTINELL® (NICOTINE) 2MG AND 4MG LOZENGES

1 NAME OF THE MEDICINE

Nicotine as nicotine polacrilex

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 2mg lozenge contains 2mg nicotine (as 13.33mg nicotine polacrilex) and each 4mg lozenge contains 4mg nicotine (as 26.660mg nicotine polacrilex).

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Nicotinell® Lozenges are cream/white embossed biconvex round tablets with an odour of peppermint. The 2mg lozenges are embossed with 'L344' and the 4mg lozenges with 'L873' on one face.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Nicotinell® Lozenges are indicated for the relief of nicotine withdrawal symptoms including cravings associated with smoking cessation. Nicotinell® Lozenges may also be used as part of a smoking reduction strategy by smokers who are unable or not ready to stop smoking abruptly as a step towards stopping smoking. The lozenges should preferably be used in conjunction with a behavioural support program.

4.2 DOSE AND METHOD OF ADMINISTRATION

Adults (18 years and over, including the elderly), who want to stop in a few months:
Nicotinell® Lozenges 2mg are suitable for smokers who have their first cigarette of the day more than 30 minutes after waking up.

Nicotinell® Lozenges 4mg are suitable for smokers who have their first cigarette of the day within 30 minutes of waking up.

Users should make every effort to stop smoking completely during treatment with Nicotinell® Lozenges. Behavioural therapy, advice and support will normally improve the success rate.

Nicotinell® Lozenges should be used according to the following schedule:
Weeks 1 to 6: 1 lozenge every 1 to 2 hours
Weeks 7 to 9: 1 lozenge every 2 to 4 hours
Weeks 10 to 12: 1 lozenge every 4 to 8 hours
To help stay smoke free over the next 12 weeks, take 1 lozenge in situations when strongly tempted to smoke.

During the initial treatment period (weeks 1 to 6) it is recommended that users take a minimum of nine lozenges per day.

For adult smokers who want to stop over several months:
Use a lozenge whenever you have a strong urge to smoke instead of smoking a cigarette. When you have reduced the number of cigarettes you smoke each day to a level from which you feel you can quit completely then use the schedule in the section above for smokers who want to quit in a few months. See your pharmacist or doctor if you have not reduced the number of cigarettes you smoke each day after 6 weeks, or if you have not begun an attempt to quit completely after 6 months.

Do not use more than 1 lozenge at a time and do not use more than 15 lozenges per day.

Patients who require NRT beyond 9 months should seek additional help and advice from a healthcare professional.

Directions for use
One lozenge should be placed in the mouth and allowed to dissolve. Periodically, the lozenge should be moved from one side of the mouth to the other, and repeated, until the lozenge is completely dissolved (approximately 20 – 30 minutes). The lozenge should not be sucked, chewed or swallowed whole.

Users should not eat or drink while a lozenge is in the mouth.

Children and adolescents
Data is limited in relation to the value of NRT use in young people where the demand for cessation products and the motivation to quit is low. Nevertheless NRT is safe in this group. NRT should only be used by adolescents in conjunction with a counselling program. Counselling is needed in this age group because NRT is likely to be ineffective in the absence of counselling.

Adolescents (12-17 years) should follow the schedule of treatment for adults above for step 1, 2 and 3, but as data is limited, duration of NRT in this age group is restricted to 12 weeks. If longer treatment is required advice from a healthcare professional should be sought who can then reassess the patient for their commitment to quitting and the benefits of continued treatment. If treatment is continued it should not be extended for more than another four weeks.

Nicotinell® Lozenges are not recommended for use in children under 12 years of age.

4.3 CONTRAINDICATIONS

Nicotinell® Lozenges are contraindicated in:

- patients with phenylketonuria;
- patients hypersensitive to nicotine or any of the excipients;
- non-smokers and children under 12 years of age (see 4.4 Special Warnings And Precautions For Use - Paediatric Use);

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Identified precautions

The risks associated with the use of Nicotine Replacement Therapy (NRT) are substantially outweighed in virtually all circumstances by the well established dangers of continued smoking.

*Patients hospitalized for myocardial infarction, severe dysrhythmia or cerebrovascular accident*s who are considered to be haemodynamically unstable should be encouraged to stop smoking with non-pharmacological interventions. If this fails, Nicotinell® Lozenges may be considered, but as data on safety in this patient group are limited, initiation should only be under medical supervision. Use with caution in patients with recent or unstable cardiovascular disease, do not continue NRT if the patient continues to smoke.

Diabetes Mellitus: Patients with diabetes mellitus should be advised to monitor their blood sugar levels more closely than usual when NRT is initiated as catecholamines released by nicotine can affect carbohydrate metabolism and vasoconstriction may delay/reduce insulin absorption.

*Allergic reactions: NRT should be used with caution by patients s*usceptible to angioedema and/or urticaria.

A risk/benefit assessment should be made by an appropriate healthcare professional for patients with the following conditions:

Phaeochromocytoma and uncontrolled hyperthyroidism: Use with caution in patients with uncontrolled hyperthyroidism or phaeochromocytoma as nicotine causes release of catecholamines.

Gastrointestinal disease: Swallowed nicotine may exacerbate symptoms in patients suffering from oesophagitis, gastric or peptic ulcers. Oral NRT should be used with caution in these conditions. Ulcerative stomatitis has been reported.

Transferred dependence: Transferred dependence is rare and is both less harmful and easier to break than smoking dependence.

Phenylketonuria: Nicotinell® Lozenges are sugar free, but do contain aspartame which metabolises to phenylalanine, which is of relevance for those with phenylketonuria.

Sodium content: Each Nicotinell® Lozenge contains 15mg of sodium (total of 225mg of sodium per maximum daily dose of 15 lozenges). People on a low sodium diet should take this into account.

Use in hepatic impairment

Use with caution in patients with moderate to severe hepatic impairment as the clearance of nicotine or its metabolites may be decreased with the potential for increased adverse events.

Use in renal impairment

Use with caution in patients with severe renal impairment as the clearance of nicotine or its metabolites may be decreased with the potential for increased adverse events.

Use in the elderly

See Section 4.2 Dose and method of administration.

Paediatric use

Danger in small children

Doses of nicotine that are tolerated by adult and adolescent smokers during treatment can produce severe symptoms of poisoning in small children and may be fatal. Products should not be left where they may be misused, handled or ingested by children.

Herron Nicaway Lozenges are not recommended for use in children under 12 years of age (see section 4.2 Dose and Method of Administration).

For use in adolescents (12-17 years), see section 4.2 Dose and Method of Administration.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No clinically relevant interactions between NRT and other drugs have definitely been established, however nicotine may possibly enhance the haemodynamic effects of adenosine.

Smoking cessation, with or without nicotine replacement, may alter the individual's response to concomitant medication and may require adjustment of dose.

Polycyclic aromatic hydrocarbons in tobacco smoke induce the metabolism of drugs catalysed by CYP 1A2 (and possibly by CYP 1A1). When a smoker stops this may result in a slower metabolism and a consequent rise in blood levels of such drugs.

The following drugs may require adjustment in dose at cessation of smoking: caffeine, theophylline, imipramine, pentazocine, tacrine, clomipramine, insulin, clozapine, olanzapine and fluvoxamine. In particular, anticonvulsants may require special monitoring and/or dosage adjustment.

Other reported effects of smoking include reduced analgesic efficacy of propoxyphene, reduced diuretic response to frusemide and altered pharmacological response to propranolol, as well as altered rates of ulcer healing with H2-antagonists. Both smoking and nicotine can increase levels of circulating cortisol and catecholamines. Dosages of nifedipine, adrenergic agonists or adrenergic blocking agents may need to be adjusted.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Effects on fertility have not been established.

Use in pregnancy – Pregnancy Category D

Smoking during pregnancy is associated with risks such as intra-uterine growth retardation, premature birth or stillbirth. Stopping smoking is the single most effective intervention for improving the health of both pregnant smoker and her baby. The earlier abstinence is achieved the better.

In studies in pregnant animals, nicotine showed maternal toxicity and consequential mild fetal toxicity. Additional effects included prenatal and postnatal growth retardation and delays and changes in postnatal CNS development. Effects were only noted following exposure to nicotine at levels in excess of those from recommended use of nicotine lozenges.

Ideally smoking cessation during pregnancy should be achieved without NRT. However for women unable to quit on their own, NRT may be recommended to assist a quit attempt. The risk of using NRT to the foetus is lower than that expected with tobacco smoking, due to lower maximal plasma nicotine concentration and no additional exposure to polycyclic hydrocarbons and carbon monoxide. However, as nicotine passes to the foetus affecting breathing movements and has a dose dependent effect on placental/foetal circulation, the decision to use NRT should be made as early on in the pregnancy as possible. The aim should be to use NRT for only 2-3 months.

While no data exists to support one form of NRT over another, intermittent dosing products may be preferable as these usually provide a lower daily dose of nicotine than patches. However, patches may be preferred if the woman is suffering from nausea during pregnancy. If patches are used they should be removed before going to bed.

Due to an absence of specific studies, combination therapy with patches and oral forms is not recommended during pregnancy unless the healthcare professional considers it necessary to ensure abstinence.

Use in lactation.

Nicotine from smoking and NRT is found in breast milk. However the amount of nicotine the infant is exposed to is relatively small and less hazardous than the second-hand smoke they would otherwise be exposed to. Using intermittent dose NRT preparations, compared with patches, may minimize the amount of nicotine in the breast milk as the time between administrations of NRT and feeding can be more easily prolonged.

Due to an absence of specific studies, combination therapy with patches and oral forms is not recommended during lactation unless the healthcare professional considers it necessary to ensure abstinence.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Used as recommended there are minimal risks associated with the use of Nicotinell® Lozenges in driving vehicles or operating machinery.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

NRT can cause adverse reactions similar to those associated with nicotine administered in other ways, including smoking. These may be attributed to the pharmacological effects of nicotine, which are dose dependent. At recommended doses Nicotinell® Lozenges have not been found to cause any serious adverse effects. Excessive consumption of Nicotinell® Lozenges by those who have not been in the habit of inhaling tobacco smoke could possibly lead to nausea, faintness or headaches.

Related adverse events with ≥ 1% excess in active compared to placebo group in a controlled study.

Very common (>1/10)
Gastrointestinal system disorders: nausea; hiccup, flatulence.

Common (>1/100; <1/10)
Psychiatric disorders: insomnia.
Central and peripheral nervous system disorders: dizziness; headache.
Respiratory system disorders: coughing; pharyngitis; sore throat.
Vomiting; constipation, diarrheoa; dysphagia; dyspepsia; heartburn; indigestion; belching; mouth irritation, mouth ulceration; tongue ulceration; dry mouth; bloating.
Uncommon (>1/1000; <1/100)
Platelet, bleeding and clotting disorders: gingival bleeding.
Metabolic and nutritional disorders: thirst; excessive thirst.
Psychiatric disorders: anxiety; anxiety attack; anxiety reaction; nightmares; marked restlessness; decreased appetite; lost appetite; lethargy.
Nervous system disorders: migraine; mucosal burning; burning sensation; paraesthesia mouth; sensory disturbance; hyperalertness.
Respiratory system disorders: dyspnoea; shortness of breath; aggravated cough; lower respiratory tract infection; respiratory disorder; excessive sneezing.
Gastrointestinal: gastroesophageal reflux; oesophageal reflux aggravated; retching; eructation; gagging; catarrh; increased saliva; lip ulceration; GI disorder; abdominal griping; sore lips; dry throat.
Special senses: taste perversion.
Skin: itching; rash.
Body as a whole: throat swelling; chest pain; tightness of chest; overdose effect; withdrawal syndrome; malaise; hot flushes; halitosis.

Certain symptoms which have been reported such as depression, irritability, anxiety and insomnia may be related to withdrawal symptoms associated with smoking cessation. Patients quitting smoking by any means could expect to suffer from headache, dizziness, sleep disturbances, increased coughing or a cold. One case has been reported of a patient who experienced restriction of her windpipe after using lozenges; the symptoms returned on re-exposure.

Nicotinell® Lozenges have similar topical effects as other oral NRT products such as mouth irritation and throat burning.

Nicotinell® Lozenges have similar cardiovascular reactions as nicotine gum i.e. rapid or irregular heartbeat, paraesthesia (oral), palpitation as less common *(>1/1000; <1/100)* and reversible atrial fibrillation as a rare *(<1/1000)* reaction.

Reporting suspected adverse effects
Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Even small quantities of nicotine may be dangerous in children. If poisoning is suspected in a child, a doctor must be consulted immediately.

The minimum lethal dose of nicotine in a non-tolerant man has been estimated to be 40 to 60mg (<1mg/kg).

Symptoms: Symptoms of acute nicotine poisoning include nausea, salivation, abdominal pain, diarrhoea, sweating, headache, dizziness, disturbed hearing and marked weakness. In extreme cases, these symptoms may be followed by hypotension, rapid or weak or irregular pulse, breathing difficulties, prostration, circulatory collapse and terminal convulsions.

All nicotine intake should stop immediately and the patient should be treated symptomatically. Artificial respiration should be instituted if necessary. Activated charcoal reduces the gastro-intestinal absorption of nicotine.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

The actions of nicotine in humans are complex, depending on dose, rate of delivery, prevalent autonomic tone, individual variation and prior exposure (tolerance).

Nicotine is the major pharmacologically active alkaloid of tobacco. The free alkaloid is absorbed rapidly through the skin and respiratory tract.

Nicotine, the chief alkaloid in tobacco products, binds stereoselectively to acetylcholine receptors at the autonomic ganglia, in the adrenal medulla, at neuromuscular junctions and in the brain. Two types of central nervous system effects are believed to be the basis of nicotine's positively reinforcing properties. A stimulating effect exerted mainly in the cortex via the locus ceruleus, produces increased alertness and cognitive performance. A 'reward' effect via the 'pleasure system' in the brain is exerted in the limbic system. At low doses the stimulant effects predominate, while at high doses the reward effects predominate.

Intermittent intravenous administration of nicotine activates neurohormonal pathways, releasing acetylcholine, noradrenaline, dopamine, serotonin, vasopressin, β-endorphin, growth hormone, and ACTH.

The cardiovascular effects of nicotine include peripheral vasoconstriction, tachycardia, and elevated blood pressure. Acute and chronic tolerance to nicotine develops from smoking tobacco or ingesting nicotine preparations. Acute tolerance (a reduction in response for a given dose) develops rapidly (less than one hour), but at distinct rates for different physiological effects (skin temperature, heart rate, subjective effects). Withdrawal symptoms, such as cigarette craving, can be reduced in some individuals by plasma nicotine levels lower than those for smoking.

Withdrawal from nicotine in addicted individuals is characterised by craving, nervousness, restlessness, irritability, mood lability, anxiety, drowsiness, sleep disturbances, impaired concentration, increased appetite, minor somatic complaints (headache, myalgia, constipation, fatigue) and weight gain. Nicotine toxicity is characterised by nausea, abdominal pain, vomiting, diarrhoea, diaphoresis, flushing, dizziness, disturbed hearing and vision, confusion, weakness, palpitations, altered respiration and hypotension.

Clinical trials

A multicentre, double blind, placebo controlled, randomised, parallel group study assessed the efficacy of 2 and 4mg nicotine lozenges in smokers wanting to quit. Treatment allocation was based on time to first cigarette (TTFC). Those smoking within 30 minutes of waking were allocated to the 4mg group (or matching placebo) and those smoking more than 30 minutes after waking were allocated to the 2mg group (or matching placebo).

The study was undertaken in the USA and the UK. A total of 1,818 smokers motivated to stop and aged over 18 years were randomised; 459 in the 2mg active group, 458 in the 2mg placebo, 450 in the 4mg active and 451 in the 4mg placebo.

Subjects were given clear instructions on how to suck the lozenge. Treatment instructions were to use one lozenge every one to two hours for the first six weeks, one lozenge every two to four hours for weeks 7 to 9, and one lozenge every four to eight hours for weeks 10 to 12. Thereafter subjects were advised to use one to two lozenges per day as needed to remain abstinent. During the first six weeks, subjects were advised to use a minimum of nine lozenges daily. At the end of six months subjects were told to refrain from taking the lozenge.

Six week, three month and six month, continuous, biochemically confirmed smoking cessation rates presented by treatment group are tabulated below.

	2mg nicotine lozenges		**4mg nicotine lozenges**	
	Active n = 459	Placebo n = 458	Active n = 450	Placebo n = 451
6 weeks	46.0%	29.7%	48.7%	20.8%
3 months	34.4%	21.6%	35.3%	14.0%
6 months	24.2%	14.4%	23.6%	10.2%

Table 1 - Smoking Cessation Rates

In a single clinical study 4mg nicotine lozenges have been shown to attenuate cessation related weight gain in high dependency smokers during the 12 week treatment period. Weight gain was reduced from a mean 2.30kg (range -3.6 to 7.3kg) in placebo lozenge users to 1.27kg (range -3.7 to 9.9kg) in 4mg lozenge users after six weeks use; and reduced from 3.40kg (range -2.2 to 10.9kg) in placebo users to 2.67kg (range -4.2 to 14.5kg) in 4mg lozenge users after 3 months lozenge use. Weight gain rebounded to at least placebo levels after termination of lozenge use in subjects continuing to refrain from smoking.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Nicotinell® Lozenges completely dissolve in the oral cavity, and the entire amount of nicotine contained in the lozenges becomes available for buccal absorption or ingestion (swallowing). The complete dissolution of Nicotinell® Lozenges is typically achieved in 20-30 minutes.

The mean Cmax and AUC (0 to infinity) was approximately 8 to 10% and 25 to 27%, respectively, higher for the lozenge compared to the equivalent dose of the gum.

Ingestion of nicotine lozenges not following dosing instructions (chewed, retained in the mouth, and swallowed; chewed and immediately swallowed) does not result in faster or higher absorption, but a substantial amount of nicotine (80-93%) is still absorbed.

Single dose studies

Single dose studies have demonstrated an increased Cmax and AUC and prolonged Tmax for both 2 and 4mg lozenge in comparison to the equivalent dose of nicotine gum. The differences were statistically significant. Mean (SD) pharmacokinetic parameters for plasma nicotine from the single dose studies are tabulated below.

Pharmacokinetic parameters	2mg nicotine lozenge	2mg nicotine gum	4mg nicotine lozenge	4mg nicotine gum
C_{max} (ng/mL)	4.4 (1.7)	4.0 (1.5)	10.8 (4.7)	10.0 (2.9)
T_{max} (hour)	1.0 (0.9)	0.8 (0.2)	1.1 (0.3)	0.9 (0.2)
AUC $_{0-\infty}$ (ng.hr/mL)	14.1 (9.2)	11.3 (7.6)	44.0 (26.5)	34.6 (17.6)

Table 2 - Pharmacokinetic Parameters

Repeat dose study

Steady state pharmacokinetic parameters for plasma nicotine have been measured after administration of 2 or 4mg nicotine lozenges every 90 minutes and the corresponding strength of nicotine gum every 60 minutes. Single dose studies had shown a higher extent of nicotine absorption when administered via a lozenge compared to a gum. To compensate for this difference, this multiple dose study was designed to utilise different intervals, i.e. every 90 minutes for lozenges and every 60 minutes for gums. The steady state levels achieved with these dosing regimens, however, showed lower steady state plasma concentrations with lozenges compared to gums, which indicated that applying different dosing intervals had a greater influence on the steady state nicotine level than the degree of absorption from the individual dose.

Distribution

As the plasma protein binding of nicotine is low (4.9% - 20%), the volume of distribution of nicotine is large (2.5 L/kg). The distribution of nicotine to tissue is pH dependent, with the highest concentrations of nicotine found in the brain, stomach, kidney and liver.

Metabolism

Nicotine is extensively metabolized to a number of metabolites, all of which are less active than the parent compound. The metabolism of nicotine primarily occurs in the liver, but also in the lung and kidney. Nicotine is metabolized primarily to cotinine but is also metabolized to

nicotine N′-oxide. Cotinine has a half-life of 15-20 hours and its blood levels are 10 times higher than nicotine. Cotinine is further oxidized to trans-3′-hydroxycotinine, which is the most abundant metabolite of nicotine in the urine. Both nicotine and cotinine undergo glucuronidation.

Excretion

The elimination half-life of nicotine is approximately 2 hours (range 1 - 4 hours). Total clearance for nicotine ranges from approximately 62 to 89 L/hr. Non-renal clearance for nicotine is estimated to be about 75% of total clearance. Nicotine and its metabolites are excreted almost exclusively in the urine. The renal excretion of unchanged nicotine is highly dependent on urinary pH, with greater excretion occurring at acidic pH.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Nicotine and cotinine were not mutagenic in the Ames Salmonella test. Nicotine induced repairable DNA damage in an E. coli test system. Nicotine was shown to be genotoxic in a test system using Chinese hamster ovary cells. In rats and rabbits, implantation can be delayed or inhibited by a reduction DNA synthesis that appears to be caused by nicotine. Studies have shown a decrease in litter size in treated with nicotine during gestation.

Carcinogenicity

Nicotine itself does not appear to be a carcinogen in laboratory animals. However, nicotine and its metabolites increased the incidence of tumours in the cheek pouches of hamsters and forestomach of F344 rats, respectively, when given in combination with tumour initiators. One study, which could not be replicated, suggested that cotinine, the primary metabolite of nicotine, may cause lymphoreticular sarcoma in the large intestine in rats.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The lozenges also contain the following inactive ingredients: Mannitol, Magnesium stearate, Sodium alginate, Xanthan gum, Potassium bicarbonate, Sodium carbonate anhydrous, Aspartame and Flavour – Peppermint (PI 106645).

Refer to Section 2 - Qualitative and quantitative composition.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

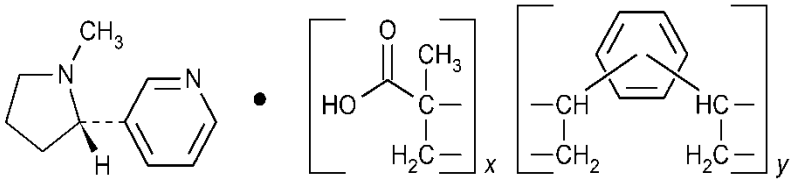
They are available in pack of 36, 72, 96, 108, 120, 132, 144, 156, 168 and 216 lozenges (not all pack sizes may be marketed).

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



CAS number

96055-45-7

7 MEDICINE SCHEDULE (POISONS STANDARD)

Not scheduled

8 SPONSOR

Perrigo Australia
25 – 29 Delawney Street
Balcatta WA
6021

9 DATE OF FIRST APPROVAL

23 June 2016

10 DATE OF REVISION

27 September 2018

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
ALL	Updated to new PI Format