Australian Product Information

NICORETTE® INHALATOR (NICOTINE)

1 NAME OF THE MEDICINE

Nicotine

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

NICORETTE® Inhalator contains nicotine 15mg per cartridge.

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

3 PHARMACEUTICAL FORM

Buccal inhalation cartridge.

NICORETTE Inhalator consists of a white to slightly coloured porous plug of polyethylene which contains nicotine and menthol. The plug is packaged in a transparent plastic tube (cartridge) which is sealed at both ends with aluminium foil. Prior to use the cartridge is inserted in a mouthpiece and the seals are broken. When air is drawn through the plug gaseous nicotine and menthol are released.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

For the treatment of tobacco dependence by relieving nicotine craving and withdrawal symptoms, thereby facilitating smoking cessation in smokers motivated to quit.

In smokers currently unable or not ready to stop smoking abruptly, NICORETTE® Inhalator may also be used as part of a smoking reduction strategy as a step towards stopping completely.

4.2 DOSE AND METHOD OF ADMINISTRATION

Smoking cessation
The dose to be used depends on the smoking habits of the individual**.** Patients may self titrate to the level of nicotine they require when they feel an urge for a cigarette or feel the onset of withdrawal symptoms. The inhalator may need to be used for a few times before an individual feels at ease using it or develops a pattern that best overcomes their craving.

After removing the mouthpiece and the sealed blister tray from the box the mouthpiece is separated into two parts and the seal is removed from the tray. One sealed cartridge is removed from the blister tray and inserted in the mouthpiece. The tray with remaining cartridges is returned to the box. When the mouthpiece is re-assembled the seal on both ends of the cartridge is broken. As air is inhaled through the cartridge the nicotine is vapourised and absorbed in the mouth.

Advice and support normally improve the success rate.

Children
NICORETTE® Inhalator should not be administered to children under 12 years of age.

Adults and elderly
It is recommended that 3-6 cartridges are used each day. Heavy smokers should use up to 6 cartridges each day.

The inhalator can be used intensely or with a slower technique that more closely mimics cigarette smoking. The technique to be used will depend on individual preference and smoking habit.

The NICORETTE® Inhalator should be used in the same way as a cigarette. Since the amount of nicotine from a puff of the inhalator is much less than that of a cigarette, about 8-10 times as many puffs compared to that when smoking a cigarette should be used (if a cigarette is smoked in 8 puffs, 64-80 puffs on the inhalator substitutes one cigarette) to reach a suitable substitution degree. Each cartridge substitutes seven cigarettes (7 sessions with 80 puffs), after which it should be replaced with a new cartridge. If craving relief is not sufficient, the number of puffs, size of the puffs or how often the NICORETTE® Inhalator is used should be increased.

No more than 6 cartridges should be used in a 24-hour period.

The cartridges in the inhalator should be regularly changed. Some individuals may benefit from using 1-2 cartridges at regular intervals such as in the morning, lunchtime and in the evening.

Normally the treatment period is 3 months. After that the dosage is gradually reduced during 6-8 weeks. Regular use of the inhalator beyond 12 months is generally not recommended. Some ex-smokers may need longer treatment with the inhalator to avoid returning to smoking. Any remaining cartridges should be retained in event of sudden cravings.

After use the cartridge is removed from the mouthpiece and disposed of. The mouthpiece should be stored in the box for further use.

Adolescents (12 to 18 years)
When deciding whether to recommend NRT an assessment should be made on the individual's nicotine dependence, motivation to quit and willingness to accept counseling. Counseling is considered to be vitally important in the effective treatment of tobacco dependence in this age group.

The dose and method of use are as for adults however as data on use of NRT in this age group are limited, the recommended duration of treatment is 12 weeks. If longer treatment is required, advice should be sought from a healthcare professional.

Combination Treatment
Combination therapy may be needed by some patients who have relapsed in the past or if they experience cravings using single therapy.

If patients have repeatedly relapsed using single therapy they should seek professional advice from their doctor or pharmacist.

NICORETTE® 15 mg Inhalator in combination with NICORETTE® 16 hr INVISIPATCH® patch can be used if breakthrough craving is experienced or there is difficulty in controlling cravings for cigarettes. In people who have been unable to quit smoking using single NRT, the combination is more effective than either product alone, increasing the patient's chances of successfully quitting.

The NICORETTE® 16 hr INVISIPATCH® patch should be applied to an intact area of the skin upon waking and removed at bedtime. After applying the NICORETTE® 16 hr INVISIPATCH® patch, the NICORETTE® 15 mg Inhalator should be used as required when cravings occur (usual dose 2-3 inhalator cartridges per day; maximum 6 cartridges per day).

For heavier smokers (more than 15 cigarettes a day): use one NICORETTE® 25 mg/16 hr INVISIPATCH® patch per day for 12 weeks plus the NICORETTE® 15 mg Inhalator (usual dose 2-3 inhalator cartridges per day; maximum 6 cartridges per day). After the initial 12 weeks treatment period, weaning may be done by either:

1. Using the NICORETTE® 15 mg/16 hr INVISIPATCH® patch for 2 weeks, followed by the NICORETTE® 10 mg/16 hr INVISIPATCH® patch for 2 weeks, while maintaining the number of inhalator cartirdges that have been routinely used; then gradually reducing the number of inhalator cartridges once the patch is no longer used; OR

2. Stopping use of the NICORETTE® 25 mg/16 hr INVISIPATCH® patch, and then gradually reducing the number of inhalator cartridges.

For lighter smokers (less than 15 cigarettes a day): use one NICORETTE® 15 mg/16 hr INVISIPATCH® patch per day for 12 weeks plus the the NICORETTE® 15 mg Inhalator (usual dose 2-3 inhalator cartridges per day; maximum 6 cartridges per day). After the initial 12 weeks treatment period, weaning may be done by either:

1. Using the NICORETTE® 10 mg/16 hr INVISIPATCH® patch for 4 weeks, while maintaining the number of inhalator cartridges that have been routinely used; then gradually reducing the number of inhalator cartridges once the patch is no longer used; OR

2. Stopping use of the NICORETTE® 15 mg/16 hr INVISIPATCH® patch, and then gradually reducing the number of inhalator cartridges.

Smoking Reduction (Reducing to Stop)
The smoker should use NICORETTE® Inhalator between smoking episodes in order to prolong intervals between cigarettes, with the aim of reducing smoking as much as possible. Not more than 6 cartridges should be used per day.

If the smoker has not achieved a reduction in the number of cigarettes per day after 6 weeks, he or she should consult a healthcare professional. This six-week time period is given to the smoker to allow them to familiarise themselves with NICORETTE® Inhalator and to deal with craving symptoms while they attempt to reduce their smoking.

Smokers who do reduce their smoking with NICORETTE® Inhalator should make a cessation attempt as soon as they feel ready, but not later than 6 months after they start using NICORETTE® Inhalator.

When making a cessation attempt, the smoking cessation instructions, above, can be followed.

If the smoker has not made a cessation attempt within 9 months of commencing treatment he or she should consult a healthcare professional.

4.3 CONTRAINDICATIONS

NICORETTE® Inhalator should not be administered to non-tobacco users or patients with known hypersensitivity to nicotine or menthol.

Use in Children
NICORETTE® Inhalator should not be administered to children under 12 years of age.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Any risks that may be associated with NRT are substantially outweighed by the well established dangers of continued smoking.

Chronic throat or bronchial disease
NICORETTE® Inhalator should be used with caution by patients with chronic throat diseases or asthma.

Underlying cardiovascular disease
In stable cardiovascular disease NICORETTE® Inhalator presents a lesser hazard than continuing to smoke. However dependent smokers with a recent myocardial infarction, unstable or worsening angina including Prinzmetal's angina, severe cardiac arrhythmias, uncontrolled hypertensions or cerebrovascular accident (CVA) and who are considered to be haemodynamically unstable should be encouraged to stop smoking with non-pharmacological interventions (such as counseling). If this fails, NICORETTE® Inhalator may be considered, but as data on safety in this patient group are limited, initiation should only be under medical supervision.

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.

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

NICORETTE® Inhalator should be avoided if oral or pharyngeal inflammation is present.

Use in renal impairment
NICORETTE® Inhalator should be used 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 effects.

Use in hepatic impairment
NICORETTE® Inhalator should be used 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 effects.

Phaeochromocytoma and uncontrolled hyperthyroidism
Nicotine, from both NRT and smoking, causes the release of catecholamines from the adrenal medulla. Therefore, NICORETTE® Inhalator should be used with caution in patients with uncontrolled hyperthyroidism or phaeochromocytoma.

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

Danger in small children
Doses of nicotine tolerated by adult and adolescent smokers can produce severe toxicity in small children that may be fatal. Products containing nicotine should not be left where they may be misused, handled or ingested by children. If a child swallows, chews or sucks the nicotine plug (used as well as unused) there is a risk of poisoning the child. Nicotine inhalators should be disposed of with care.

Use in the elderly
A minor reduction in total clearance of nicotine has been demonstrated in healthy elderly patients, however, not justifying an adjustment of dosage.

Paediatric use
NICORETTE® Inhalator should not be administered to children under 12 years of age.
For use in adolescents (12-18 years), see section 4.2 Dose and Method of Administration.

Continued smoking while using NRT
NICORETTE® Inhalator can safely be used while smoking. The adverse event profile (incidence and severity of events) of NICORETTE® Inhalator in studies to reduce smoking did not differ markedly from that in smoking cessation studies. Intermittent use of NICORETTE® Inhalator and cigarettes does not appear to produce more side effects than use of NRT alone. Most regular smokers are adept at self-titration of their nicotine intake in order to maintain their plasma nicotine levels within a narrow range.

Effects on laboratory tests
No data available.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No clinically relevant interactions between nicotine replacement therapy and other drugs have definitely been established. However nicotine may possibly enhance the haemodynamic effects of adenosine i.e. increase in blood pressure and heart rate and also increase pain response (angina-pectoris type chest pain) provoked by adenosine administration.

Stopping smoking
Polycyclic aromatic hydrocarbons in tobacco smoke induce the metabolism of drugs metabolised by CYP 1A2 (and possibly by CYP 1A1). When a smoker stops smoking, this may result in slower metabolism and a consequent rise in blood levels of such drugs. This is of potential clinical importance for products with a narrow therapeutic window, e.g. theophylline, clozapine and ropinirole.

The plasma concentration of other drugs metabolised in part by CYP1A2, for example imipramine, olanzapine, clomipramine, fluvoxamine and caffeine may also increase on cessation of smoking, although data to support this are lacking and the possible clinical significance of this effect is unknown.

Limited data indicate that the metabolism of flecainide and pentazocine may also be induced by smoking.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility
Studies have shown a decrease of litter size in rats treated with nicotine during the time of fertilisation.
Use in pregnancy: Category D
Nicotine is harmful to the foetus. The harmful effects of cigarette smoking on maternal and foetal health are clearly established. Short-term exposure during the first trimester is unlikely to cause a hazard to the foetus.

NRT is not contraindicated in pregnancy. The decision to use NRT should be made on a risk-benefit assessment as early on in the pregnancy as possible with the aim of discontinuing use as soon as possible.

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.

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.

Nicotine passes to the foetus affecting breathing movements and has a dose-dependent effect on placental/foetal circulation. However, the risk of using NRT to the fetus 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.

Intermittent dosing products such as NICORETTE® Chewing Gums, Lozenges, Mouth Spray or Inhalator, 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.

Use in lactation
NRT is not contraindicated 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, such as NICORETTE® Chewing Gums, Lozenges, Mouth Spray or Inhalator, may minimize the amount of nicotine in the breast milk as the time between administrations of NRT and feeding can be more easily prolonged. Women should breastfeed just before using the product

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

NICORETTE® Inhalator may cause adverse reactions similar to those associated with nicotine administered by other means, such as gum, lozenges, mouth spray and patch and are dose-dependent.

About 40% of treated patients experience side effects in the form of local reactions such as cough and irritation in the mouth and throat, respectively, during the initial term of treatment. Those side effects decrease gradually during the first weeks of treatment.

Some symptoms, such as dizziness, headache and sleeplessness may be related to withdrawal symptoms associated with abstinence from smoking. Increased frequency of aphthous ulcer may occur after abstinence from smoking. The causality is unclear.

Clinical Trial Data

The safety of nicotine from clinical trial data is based on data on a meta-analysis of randomized clinical trials (RCTs) for the treatment of smoking cessation. Adverse Drug Reactions (ADRs) with oromucosal formulations identified from clinical trials are presented below in Table 1.

Table 1. ADRs Reported with a Frequency ≥1% Identified from Meta-analysis of Clinical Trial Data with Nicotine Oromucosal Formulations

System Organ Class Preferred Term	Active N = 3914(%)	Placebo N = 2819 (%)
Gastrointestinal Disorders		
Abdominal Pain	1.8	1.2
Dry Mouth	3.2	2.7
Dyspepsia	6.1	3.3
Flatulence	1.8	1.4
Nausea[a]	10.4	5.8
Salivary hypersecretion	2.6	1.0
Stomatitis	2.6	2.0
Vomiting[a]	2.7	1.2
General Disorders and Administration Site Conditions		
Fatigue[a]	1.0	0.6
*Burning sensation**	1.0	0.5
Immune System Disorders		
Hypersensitivity[a]	1.4	1.22
Nervous System Disorders		
Headache[a#]	11.5	13.0
Paraesthesia[a]*	1.3	0.8
Dysgeusia	3.2	2.8
Respiratory, Thoracic and Mediastinal Disorders		
*Cough***	9.3	10.7
*Hiccups****	16.4	2.3
*Throat irritation***	11.8	4.4

[a] Systemic effects
*At the application site
** Higher frequency observed in clinical studies with inhaler formulation
*** Higher frequency observed in clinical studies with mouth spray formulation
[#] Although the frequency in the active group is less than that of the placebo group, the frequency in the specific formulation in which the PT was identified as a systemic ADR was greater in the active group than the placebo group.

Post Marketing Data
ADRs first identified during post-marketing experience with nicotine are presented in Table 2. Frequencies are provided according to the following convention:

Very common	≥1/10
Common	≥1/100 and < 1/10
Uncommon	≥1/1,000 and <1/100
Rare	≥1/10,000, <1/1,000
Very rare	<1/10,000
Not known	(cannot be estimated from the available data)

Table 2. ADRs Identified During Post-Marketing Experience with Nicotine Oromucosal Formulations with Frequency Category Estimated from Clinical Trials

System Organ Class Frequency category	**Preferred Term**
Cardiac Disorders	
Uncommon	*Palpitations* **
Uncommon	*Tachycardia* **
Eye Disorders	
Not known	*Blurred vision*
Not known	*Lacrimation increased*
Gastrointestinal Disorders	
Common	*Diarrhoea* #
Not known	*Dry Throat*
Rare	*Dysphagia*
Uncommon	*Eructation*
Not known	*Gastrointestinal discomfort* **
Uncommon	*Glossitis*
Rare	*Hypoaesthesia oral* #
Uncommon	*Oral mucosal blistering and exfoliation*
Not known	*Lip pain*
Uncommon	*Paraesthesia oral* #
Rare	*Retching*
General Disorders and Administration site Conditions	
Uncommon	*Asthenia* **
Uncommon	*Chest discomfort and pain* **
Uncommon	*Malaise* **
Immune System Disorders	
Not known	*Anaphylactic reaction* **
Musculoskeletal and Connective Tissue Disorders	
Not known	*Muscle tightness* *
Unknown	*Pain in jaw* *
Psychiatric Disorders	
Uncommon	*Abnormal dream* **,***

Respiratory, Thoracic and Mediastinal Disorders	
Uncommon	*Dyspnoea* **
Uncommon	*Bronchospasm*
Uncommon	*Dysphonia*
Uncommon	*Nasal congestion*
Uncommon	*Oropharyngeal pain*
Uncommon	*Sneezing*
Uncommon	*Throat tightness*
Skin and Subcutaneous Tissue Disorders	
Not known	*Angioedema* **
Not known	*Erythema* **
Uncommon	*Hyperhidrosis* **
Uncommon	*Pruritus* **
Uncommon	*Rash* **
Uncommon	*Urticaria* **
Vascular Disorders	
Uncommon	*Flushing* **
Uncommon	*Hypertension* **

* Tightness of jaw and pain in jaw with nicotine gum formulation
** Systemic effects
*** Systemic effect, identified only for formulations administered during night
# Reported the same or less frequently than placebo

Reporting Suspected Adverse Events
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: https://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Excessive use of nicotine from either NRT and/or smoking might cause symptoms of an overdose.

Symptoms of overdose are those of acute nicotine poisoning and include nausea, increased salivation, vomiting, abdominal pain, diarrhoea, sweating, headache, dizziness, disturbed hearing and marked weakness. At high doses, these symptoms may be followed by hypotension, weak and irregular pulse, breathing difficulties, prostration, circulatory collapse and general convulsions.

Overdose with nicotine can occur if the patient has a very low pre-treatment nicotine intake or uses other forms of nicotine. The acute minimum lethal oral dose of nicotine in non-smokers is believed to be 40-60 mg.

Doses of nicotine that are tolerated by adult smokers during treatment may produce severe symptoms of poisoning in small children and may prove fatal. The lethal dose of nicotine in a small child is approximately 10-15 mg. Suspected nicotine poisoning in a child should be considered a medical emergency and treated immediately.

A used inhalator cartridge contains about 47% of its initial nicotine content, which is about 7 mg.

Management of overdose
If a cartridge is ingested, activated charcoal should be given as soon as possible.

The administration of nicotine must be stopped immediately and the patient should be treated symptomatically. Activated charcoal reduces gastrointestinal absorption of nicotine.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Nicotine is a natural alkaloid which has ganglion stimulating properties and produces a wide range of pharmacological actions.

The use of nicotine is widespread in the form of tobacco products, chronic use of which is causally linked to a variety of serious diseases. Many smokers develop a dependence due to an interaction of pharmacological, social and psychological factors.

NICORETTE® Inhalator is a treatment-aid in smoking cessation. Clinical studies have shown that nicotine replacement from nicotine containing products can help people give up smoking by relief of abstinence symptoms associated with smoking cessation.

Abrupt cessation of the use of tobacco-containing products following a prolonged period of daily use results in a characteristic withdrawal syndrome that includes four or more of the following: dysphoria or depressed mood; insomnia; irritability, frustration or anger; anxiety; difficulty concentrating, restlessness or impatience; decreased heart rate; and increased appetite or weight gain. Nicotine craving which is recognised as a clinically relevant symptom, is also an important element in nicotine withdrawal.

Clinical studies have shown that nicotine replacement products can help smokers abstain from smoking by relieving these withdrawal symptoms.

Clinical trials

Smoking Cessation studies

No new clinical trials have been conducted on the NICORETTE® Inhalator 15 mg.

The efficacy of NICORETTE® Inhalator 10 mg has been evaluated in six controlled clinical trials that included a total of 730 subjects who used the inhalator.

The first three studies (T90NI01, T90NI02, T90NI03) are regarded as dose finding, supportive studies. In the later studies (T91NI04, 92NNIN002, 92NNIN003) the dosage recommendations were based on the analysis of the first three studies and form the basis for the efficacy evaluation. Subjects recruited in these studies had resolved to quit smoking and were provided with varying degrees of professional support.

In three studies, higher quit rates were demonstrated in the active treatment groups than in the placebo groups. The quit rate for each study, defined as complete abstinence from the end of week 2 through to week 6 no slips allowed, was for the active versus placebo group respectively; 46% active versus 33% placebo, 45% active versus 14% placebo, 44% active versus 23% placebo. The difference in all three studies was statistically highly significant.

Efficacy in completely abstinent subjects from week 2.

Quit Rates by Treatment (N= 692 Patients in 3 Studies) (T91NI04, 92NNIN002 and 92NNIN003)					
Group	**Number of Patients**	**At 6 Weeks**	**At 3 Months**	**At 6 Months**	**At 12 Months***
NICORETTE Inhalator	346	44-46%	31-37%	20-35%	11-28%
Placebo	346	14-33%	8-22%	6-19%	5-18%

*** Follow-up, patients not on treatment.**

Smoking Reduction studies

Placebo-controlled double-blind, randomised clinical studies in healthy smokers who did not intend to quit smoking but who were motivated to reduce their smoking have shown that NICORETTE® Chewing Gum (4 studies) and NICORETTE® Inhalator (2 studies) is effective at helping smokers reduce the number of cigarettes smoked, and that reducing smoking leads to the increased likelihood of smoking cessation.

Pooled data from two NICORETTE® Inhalator smoking reduction studies (96NNIN-016 & 98-NNIN-027) showed that 21.9% of subjects using the nicotine inhalator had achieved a sustained reduction in smoking (by at least 50%) at 4 months, compared to 8.7% of the placebo-treated subjects.

Pooled data from the two NICORETTE® Inhalator studies and four similarly designed NICORETTE® Gum studies showed that a total of 193/1215 (15.9%) subjects in the NICORETTE® treatment groups in the six studies managed to reduce their cigarette consumption by at least 50% from week 6 to month 4 compared to 81/1209 (6.7%) in the placebo treated groups. The point prevalence (PP) quit rates at month 12 for these individuals was 58/193 (30.1%) in the NICORETTE® treatment groups compared to 15/81 (18.5%) in the placebo treated groups.

The corresponding figures for smokers who were unable to reduce their cigarette consumption by at least 50% from week 6 to month 4 with regards to PP abstinence at month 12 were 47/1022 (4.6%) in the NICORETTE® treated groups and 39/1128 (3.5%) in the placebo treated groups.

Overall, at 1 year, 8.15% of subjects treated with NICORETTE® gum or inhalator were abstinent, compared to 4.05% of placebo-treated subjects, giving an odds ratio of 2.10 (95% confidence interval1.48, 2.99).

As regular smokers are generally adept at self-regulating their nicotine intake within a narrow range it is unlikely that concomitant use of nicotine gum or inhalator and smoking will result in overdose or plasma nicotine levels higher than those achieved with smoking alone.

During the smoking reduction studies no clinically significant treatment-related adverse events were observed during the concomitant use of gum or inhalator and cigarettes for up to 12-18 months. The adverse event profile did not differ markedly from that in smoking cessation studies.

In a 3-way open tolerability study in 19 healthy smokers investigating the concurrent use of 4 mg chewing gum and smoking during physical exercise subjects were administered each of the following treatments: placebo gum + smoking one cigarette; 4mg gum + one unlit cigarette; 4mg gum + smoking one cigarette. Each treatment was repeated 7 times during 7 consecutive hours on one day. During multiple sub-maximal exercise tests, no signs of myocardial ischemia with any

of the 3 treatments or differences between the 3 treatments in the number of extra systoles, episodes of two or more systoles or other arrhythmias were observed. Changes in mean heart rate and systolic blood pressure during exercise, and diastolic blood pressure at rest, tended to be higher in the smoking + gum group; however, the differences between treatments were minor.

Of 3,094 smokers with Chronic Obstructive Pulmonary Disease (COPD) participating in a 5-year lung health study, 25% of subjects were smoking and using gum, and 40% were abstinent and continued to use gum after 1 year. No increase in the incidence of cardiovascular events in the abstainers who used gum or in those who used gum and continued to smoke were observed.

5.2 PHARMACOKINETIC PROPERTIES

The major fraction of the nicotine in NICORETTE® Inhalator is deposited in the oral cavity. About 50 % of the releases nicotine is systemically available. Absorption of nicotine through the buccal mucosa is slow and does not produce the high and rapid nicotine plasma concentrations seen with cigarette smoking. Factors that determine the amount of nicotine released from the inhalator are the volume of air passing through the cartridge and the temperature of the air. The volume of inhalation differs between individuals.

On average, 2 mg of nicotine is released during 20 minutes of intensive use. Steady state plasma levels of approximately 20-25 ng/mL are achieved with continuous, rapid inhalations during 20 minutes per hour for 12 hours at ambient room temperature in a laboratory setting. The plasma concentrations following clinical use corresponded to once hourly chewing of NICORETTE® chewing gum 2 mg.

When used as a cigarette, taking 8 times as many puffs as when smoking, NICORETTE® Inhalator delivers about 1 mg of nicotine. When used this way a 15 mg cartridge will deliver the same amount of nicotine (about 1 mg), at a uniform release rate, for the first seven consecutive uses. Further use of the inhalator will also deliver nicotine but at a decreasing rate. A dose of 1 mg will result in a degree of nicotine substitution of about 50% compared to hourly smoking (ref: Study 98NNIN026 where the inhalator was used every hour for 12 hours, each time with 8 times as many puffs as when smoking a cigarette.)

The biologically available dose is increased by approximately 29% at 30˚C and 48% at 40˚C as compared with the available dose at 20˚C.

The therapeutic blood concentration i.e. the blood concentration level that relieves craving, is individual, based on the patient's nicotine dependence.

NICORETTE® Inhalator 15 mg results in a plasma nicotine level of about 33% of normal smoking levels. Normal smoking level is defined as 20 cigarettes/day.

Progressive severity of renal impairment is associated with decreased total clearance of nicotine. The pharmacokinetics of nicotine are unaffected in cirrhotic patients with mild liver impairment (Child score 5) and decreased in cirrhotic patients with moderate liver impairment (Child score 7). Raised nicotine levels have been seen in smoking patients undergoing haemodialysis.

The volume of distribution following IV administration of nicotine is about 2 to 3 L/kg and the half-life ranges from 2 to 3 hours. The major eliminating organ is the liver and average plasma clearance is about 70 L/hour. The kidney and lung also metabolise nicotine. More than 20 metabolites of nicotine have been identified, all of which are believed to be less active than the parent compound. The primary metabolite of nicotine in plasma, cotinine, has a half-life of 15 to 20 hours and concentrations that exceed nicotine by 10-fold.

Plasma protein binding of nicotine is less than 5%. Therefore, changes in nicotine binding from use of concomitant drugs or alterations of plasma proteins by disease states would not be expected to have significant effects on nicotine kinetics.

The primary urinary metabolites are cotinine (15% of the dose) and trans-3-hydroxy-cotinine (45% of the dose). About 10% of nicotine is excreted unchanged in the urine. As much as 30% of nicotine may be excreted unchanged in the urine with high flow rates and acidification of the urine below pH 5.

There are no differences in nicotine kinetics between men and women.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
Literature reports indicate that nicotine is neither an initiator nor a tumour promoter in mice.

Neither nicotine nor cotinine was mutagenic in the Ames Salmonella test.

Carcinogenicity
There was no evidence of carcinogenicity in rats following inhalation of nicotine for up to 2 years, associated with plasma nicotine levels of 4 times the maximum anticipated clinical level.

There is inconclusive evidence to suggest that cotinine, an oxidised metabolite of nicotine, may be carcinogenic in rats.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

NICORETTE® Inhalator in addition to the active ingredients contains menthol.

6.2 INCOMPATIBILITIES

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

6.3 SHELF LIFE

36 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25^{o}C

6.5 NATURE AND CONTENTS OF CONTAINER

NICORETTE Inhalator cartridges consist of a porous plug packaged in a transparent tube which is sealed at both ends with aluminium foil. The cartridges are supplied in a blister tray together with a mouthpiece.

Pack sizes
4 cartridges in a blister tray with a mouthpiece
6 cartridges in a blister tray with a mouthpiece
18 cartridges in a blister tray with a mouthpiece
20 cartridges in a blister tray with a mouthpiece

24 cartridges in a blister tray with a mouthpiece
42 cartridges in a blister tray with a mouthpiece

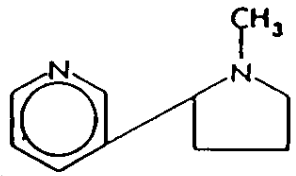
Not all pack sizes may be marketed

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSIOCHEMICAL PROPERTIES

Chemical Structure



CAS number
54-11-5

7 MEDICINE SCHEDULE (POISONS STANDARD)

Unscheduled

8 SPONSOR

Johnson & Johnson Pacific
45 Jones Street
Ultimo NSW 2007

® Registered trademark

9 DATE OF FIRST APPROVAL

27 November 2001

10 DATE OF REVISION

30 October 2019

Summary table of changes

Section changed	Summary of new information
All	Update to new PI format. Addition of more restrictive safety-related information to section 4.8.