AUSTRALIAN PRODUCT INFORMATION

NICORETTE CHEWING GUM
2mg & 4mg

1 NAME OF THE MEDICINE

Nicotine

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

NICORETTE® chewing gum contains nicotine, added as nicotine polacrilex. They are available in 2mg and 4mg strengths and are available in five flavours: classic, icymint, freshmint, spearmint and freshfruit.

NICORETTE® classic chewing gum also contains: sodium and sorbitol.

NICORETTE® freshfruit, icymint and spearmint chewing gum also contains: sucralose, sodium and xylitol.

NICORETTE® freshmint chewing gum also contains: sodium and xylitol.

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

3 PHARMACEUTICAL FORM

NICORETTE® chewing gums are square, coated pieces of gum.

NICORETTE® 2mg classic chewing gums are beige in colour.

NICORETTE® 2mg icymint, freshfruit, spearmint and freshmint chewing gums are white in colour.

NICORETTE® 4mg classic chewing gums are yellow in colour.

NICORETTE® 4mg icymint, freshfruit, spearmint and freshmint chewing gums are cream in colour.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

NICORETTE® chewing gums are indicated 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 Chewing Gum 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 initial dosage should be individualised on the basis of the patient's nicotine dependence. Nicorette Chewing Gum should be used when the urge to smoke is felt. Most smokers require about 8-12 pieces of the 2 mg gum or 4-6 pieces of the 4 mg gum. Not more than 20 pieces of the 2 mg gum or 10 pieces of the 4 mg gum (equivalent to a daily dose of 40 mg) should be chewed in one day. Highly dependent smokers (smoke >20 cigarettes/day) or patients who have failed to stop smoking with the 2mg gum should receive the 4mg dosage initially. Other patients should begin treatment with the 2mg dosage strength.

Advice and support normally improve the success rate.

The following points should be observed:
Due to their nicotine content, **NICORETTE**® chewing gum has an unusual taste. **NICORETTE**® chewing gum should be chewed slowly until a strong taste or a slight tingling sensation is felt. When the tingling sensation occurs the smoker should stop chewing and the gum should be placed under the tongue or between the cheek and gums until the taste or tingling sensation has disappeared. Chewing should then be resumed slowly and the procedure repeated. **NICORETTE**® chewing gum should be chewed in this manner until the nicotine effect is no longer experienced (about 30 minutes).

The nicotine effects are not experienced until after a few minutes of chewing, the rapid satisfaction supplied by smoking is hence not to be expected. Rapid chewing may initially irritate the throat or cause hiccups or nausea. Adapting to the proper chewing technique takes a few days. Acidic beverages, e.g., coffee or soft drinks interfere with the buccal absorption of nicotine. Use of such beverages should therefore be avoided for 15 minutes before and during chewing.

Children

NICORETTE® chewing gum should not be administered to children under 12 years of age.

Adults and elderly

The gum should be used for at least 3 months. Gradual weaning from the gum should then be initiated. Treatment should be stopped when the dose is reduced to 1-2 chewing gums per day. Any spare gum should be retained, as craving may suddenly occur.

Regular use of the gum beyond 12 months is generally not recommended. Some ex-smokers may need longer treatment with the gum to avoid returning to smoking.

Adolescents (12 to 18 years)

When deciding whether to recommend NRT an assessment should be made on the individual's nicotine dependance, motivation to quit and willingness to accept counselling. Counselling is considered to be vitally important in the effective treatment of tobacco dependence in this age group.

Use for up to 8 weeks to break the habit of smoking, then gradually reduce gum use over a 4 week period. When daily use is 1-2 gums, use should be stopped.

For those using 4 mg nicotine gum, the 2 mg nicotine gum will be helpful during withdrawal from treatment.

As data are limited in this age group, the recommended duration of treatment is 12 weeks. If longer treatment is required, advice should be sought from a healthcare professional.

Before a recommendation to extend treatment beyond 12 weeks is made the patient should be

reassessed for commitment to quitting, expected benefit of continued treatment and maturity. Treatment should not be extended by more than a further 4 weeks.

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® 2 mg chewing gum in combination with **NICORETTE**® 16hr 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 product, the combination is more effective than either product alone, increasing the patient's chances of successfully quitting.

The treatment involves the addition of **NICORETTE**® 2mg chewing gum to the patch. The **NICORETTE**® 16hr Invisipatch patch should be applied daily to an intact area of the skin upon waking and removed at bedtime, and the **NICORETTE**® 2mg chewing gum, should be used as required when cravings occur.

For heavier smokers (greater than 15 cigarettes a day): use one 25mg/16hr patch/day for 12 weeks plus the 2mg gum (at least 4 gums; usual dose 5-6 gums; maximum 12/day). After the initial 12 weeks treatment period, weaning may be done by either:
- using the 15mg/16hr patch for 2 weeks, followed by the 10mg/16hr patch for 2 weeks, while maintaining the number of 2mg gums that have been routinely used; then gradually reducing the number of gums once the patch is no longer used; or
- stopping use of the 25mg/16hr patch, and then gradually reducing the number of 2mg gums.

For lighter smokers (less than 15 cigarettes a day): use one 15mg/16hr patch/day for 12 weeks plus the 2mg gum (at least 4 gums; usual dose 5-6 gums; maximum 12/day). After the initial 12 weeks treatment period, weaning may be done by either:
- using the 10mg/16hr patch for 4 weeks, while maintaining the number of 2mg gums that have been routinely used; then gradually reducing the number of gums once the patch is no longer used; or
- stopping use of the 15mg/16hr patch, and then gradually reducing the number of 2mg gums.

The **NICORETTE**® 16hr INVISIPATCH patch should not be used with Nicorette 4 mg gum.

Smoking Reduction (Reducing to stop)
The smoker should use **NICORETTE**® chewing gum between smoking episodes in order to prolong intervals between cigarettes, with the aim of reducing smoking as much as possible. Highly dependent smokers (smoke >20 cigarettes/day) or patients who have failed to stop smoking with the 2mg gum should use the 4mg dosage. Other patients should begin treatment with the 2mg dosage. Not more than 20 pieces of the 2 mg gum or 10 pieces of the 4 mg gum (equivalent to a daily dose of 40 mg) should be chewed in one 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**® chewing gum and to deal with craving symptoms while they attempt to reduce their smoking.

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

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® chewing gum should not be administered to non-tobacco users or patients with known hypersensitivity to nicotine or any component of the chewing gum.

Use in children

NICORETTE® chewing gum 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.

Denture warning

Smokers who wear dentures may experience difficulty in chewing **NICORETTE®** chewing gum. The chewing gum may stick to, and may in rare cases damage dentures.

Underlying cardiovascular disease

In stable cardiovascular disease **NICORETTE®** chewing gum presents a lesser hazard than continuing to smoke. However dependent smokers currently hospitalised as a result of myocardial infarction, severe dysrhythmia or cerebrovascular accident (CVA) and who are considered to be haemodynamically unstable should be encouraged to stop smoking with non-pharmacological interventions. If this fails, **NICORETTE®** chewing gum 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, gastritis or peptic ulcers and oral NRT preparations should be used with caution in these conditions. Ulcerative stomatitis has been reported.

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

Phaeochromocytoma and uncontrolled hyperthyroidism

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

Epilepsy and seizures
Caution should be exercised in patients with a history of epilepsy or seizures during introduction of nicotine replacement therapy. Tobacco smoke contains substances – including nicotine – which act on brain receptors, and the changes in intake of these when switching from smoked tobacco to nicotine replacement therapy during quitting may affect seizure threshold

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

Excipients
NICORETTE® classic chewing gum contains sorbitol; patients with rare hereditary problems of fructose intolerance should not take this medicine.

NICORETTE® chewing gum also contain butylated hydroxy toluene (E321) in the gum base; this may cause irritation to the mucous membranes.

Continued smoking while using NRT
NICORETTE® chewing gum can safely be used while smoking. The adverse event profile (incidence and severity of events) of **NICORETTE®** chewing gum in studies to reduce smoking did not differ markedly from that in smoking cessation studies. Intermittent use of **NICORETTE®** chewing gum 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.

Use in hepatic impairment
NICORETTE® chewing gum 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.

Use in renal impairment
NICORETTE® chewing gum 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 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® chewing gum should not be administered to children under 12 years of age.

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. Nicotine gum should be disposed of with care.

Effects on laboratory test
No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No clinically relevant interactions between nicotine replacement therapy and other drugs has 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/fetal circulation. However 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.

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.

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, Inhalator or Mouth Spray 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
NICORETTE® chewing gum has no or negligible influence on the ability to drive and use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)
NICORETTE® chewing gum may cause adverse reactions similar to those associated with nicotine administered by other means and are mainly dose-dependent. Most of the undesirable effects reported by the patients occur during the first 3-4 weeks after start of treatment.

The chewing gum may stick to, and in rare cases may damage dentures. Irritation in the mouth and throat may be experienced, however most subjects adapt to this with ongoing use.

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 = 3214 (%)	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		
*Burning sensation**	1.0	0.5
Fatigue[a]	1.0	0.6
Immune System Disorders		
Hypersensitivity[a]	1.4	1.22
Nervous System Disorders		
Headache[a#]	11.5	13.0
Dysgeusia	3.2	2.8
Paraesthesia[a]	1.3	0.8

Respiratory, Thoracic and Mediastinal Disorders		
*Cough***	9.3	5.9
*Hiccups****	16.4	2.3
*Throat irritation***	11.8	4.4

*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***

Immune System Disorders	
Not known	*Anaphylactic reaction***
Musculoskeletal and Connective Tissue Disorders	
Not known	*Muscle tightness**
Uncommon	*Pain in Jaw**
Nervous System Disorders	
Not known	*Seizure***
Psychiatric Disorders	
Uncommon	*Abnormal dream**,***
Respiratory, Thoracic and Mediastinal Disorders	
Uncommon	*Bronchospasm*
Uncommon	*Dysphonia*
Uncommon	*Dyspnoea***
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. The risk of poisoning as a result of swallowing the gum is very small, as absorption in the absence of chewing is slow and incomplete.

Symptoms of overdosage are those of acute nicotine poisoning and include nausea, 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.

Overdosage 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.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

If chewing gum is ingested, activated charcoal should be given as soon as possible. Contact the Poisons Information Centre (131126) for advice on treatment.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Nicorette Chewing Gum 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

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 four Nicorette gum smoking reduction studies (98-NNCG-014, 980-chc-1013-28, 98-NNCG-017, 980-CHC-9021-0013) showed that 12.8% of subjects using the nicotine gum had achieved a sustained reduction (by at least 50%) in smoking at 4 months, compared to 5.7% of placebo-treated subjects.

Pooled data from the four Nicorette gum studies and two similarly designed Nicorette Inhalator 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

Nicotine administered in chewing gums is readily absorbed from the oral mucosa membranes. Demonstrable blood levels are obtained within 5-7 minutes after starting chewing and reach a maximum about 5-10 minutes after chewing is stopped. Blood levels are roughly proportional to the amount of nicotine released by chewing and are unlikely to exceed those obtained from smoking cigarettes.

The amount of nicotine extracted from one chewing gum depends on how vigorously and for how long it is chewed. The amount of nicotine absorbed depends on the amount extracted and the loss from the oral cavity due to swallowing or expectoration. The systemic availability of swallowed nicotine is lower due to first-pass hepatic metabolism. The high and rapidly rising nicotine concentration seen after smoking is rarely produced by treatment with the gum. Normally

approximately 1.4 mg and 3.4 mg of nicotine will be extracted from the 2 mg and 4 gum respectively.

Steady state trough levels of 10-14 ng/mL for 2 mg and 24-29 ng/mL for 4 mg Nicorette gum are achieved during standardised conditions i.e. chewing every two seconds for 30 minutes. A 12 week study found that 2 mg Nicorette chewing gum produced nicotine plasma levels of about 9 ng/mL, while 4 mg gum produced nicotine plasma levels of about 23 ng/mL. Afternoon peak plasma levels after cigarette smoking are about 35 ng/mL.
The volume of distribution following IV administration of nicotine is about 2 to 3 L/kg and the half-life approximately 2 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.

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.

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.

Progressive severity of renal impairment is associated with decreased total clearance of nicotine. The pharmacokinetics of nicotine is 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 hemodialysis.

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

5.3 PRECLINICAL SAFETY DATA

In vitro and *in vivo* genotoxicity testing of nicotine has yielded predominantly non- genotoxic results. Some positive findings from *in vitro* and *in vivo* genotoxicity tests have been reported but investigations using regulatory accepted assays and protocols have shown no evidence of genotoxic activity at therapeutic doses.

Analysis of the results from long-term carcinogenicity assays data with nicotine or cotinine, major nicotine metabolite, predominately indicate nicotine does not have any significant or relevant carcinogenic activity.

General toxicology
Nicotine has oral and dermal LD_{50} in the range of 70 mg/kg. The general toxicity of repeated administration of nicotine is well known. Observations in chronic 2 year dosed feeding study in rats (5 mg/kg/day) showed no evidence of toxicity or overt behavior and health including any tumor responses.

Genotoxicity
Nicotine showed negative results in *in vitro* tests but few *in vitro* and *in vivo* genotoxicity studies examining strand-breaking activity assessed by the comet assay, chromosome aberration or micronucleus formation gave positive results. However, the tested range is beyond the systemic nicotine levels achieved in humans by using nicotine products

Carcinogenicity
Long term animal studies with nicotine suggest that nicotine does not have any significant or relevant carcinogenic activity

Teratogenicity
In animal experiments nicotine induced maternal toxicity, fetal toxicity including post-implantation loss and growth retardation.

Fertility
In animal experiments, nicotine adversely affected spermatogenesis. To which extent female fertility is affected is not known.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

NICORETTE® Classic in addition to the active contains sodium carbonate, chewing gum base, sorbitol powder, sorbitol solution (70%), halverstroo flavour ZD49284, flavour for smoker 846422, glycerol.

The 2mg Classic Chewing Gum also contains sodium bicarbonate. The 4mg Classic Chewing Gum also contains quinoline yellow CI47005.

NICORETTE® Freshmint in addition to the active contains chewing gum base, xylitol, peppermint oil, sodium carbonate, acesulfame potassium, menthol, magnesium oxide light, acacia, titanium dioxide, and carnauba wax.

The 2mg Freshmint Chewing Gum also contains sodium bicarbonate. The 4mg Freshmint Chewing Gum also contains quinoline yellow CI47005.

NICORETTE® Freshfruit in addition to the active contains chewing gum base, xylitol, peppermint oil, sodium carbonate, acesulfame potassium, menthol, magnesium oxide light, acacia, titanium dioxide, carnauba wax, tuttifruitti flavour, hypromellose, sucralose, and polysorbate 80.

The 2mg Freshfruit Chewing Gum also contains sodium bicarbonate. The 4mg Freshfruit Chewing Gum also contains quinoline yellow CI47005.

NICORETTE® Icy Mint in addition to the active contains chewing gum base, xylitol, peppermint oil, sodium carbonate, acesulfame potassium, menthol, magnesium oxide light, pregelatinised maize starch, titanium dioxide, carnauba wax, winterfresh flavour, hypromellose, sucralose, and polysorbate 80.

The 2mg Icy Mint Chewing Gum also contains sodium bicarbonate. The 4mg Icy Mint Chewing Gum also contains quinoline yellow CI47005.

NICORETTE® Spearmint in addition to the active contains chewing gum base, xylitol, peppermint oil, sodium carbonate, acesulfame potassium, menthol, magnesium oxide light, acacia, titanium dioxide, carnauba wax, spearmint flavour, hypromellose, sucralose, and polysorbate 80.

The 2mg Spearmint Chewing Gum also contains sodium bicarbonate. The 4mg Spearmint Chewing Gum also contains quinoline yellow aluminium lake.

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

6.3 SHELF LIFE
NICORETTE® Classic Chewing Gum 2 mg and 4 mg: 30 months

NICORETTE® Freshmint Chewing Gum 2 mg and 4 mg: 36 months

NICORETTE® Freshfruit Chewing Gum 2 mg and 4 mg: 36 months

NICORETTE® Icy Mint Chewing Gum 2 mg and 4 mg: 36 months

NICORETTE® Spearmint Chewing Gum 2 mg and 4 mg: 36 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER
NICORETTE® Classic Chewing Gum 2 mg and 4 mg: blister packs of 15, 30, 60, 75, 105, 135, 150, 180, 200, 210, 225, 240, 255, 270, 285, 300, 310, 315, 325, 340, 355, 370, 385, 400.

NICORETTE® Freshmint Chewing Gum 2 mg and 4mg: blister packs of 15, 30, 105, 180, 200, 210, 225, 240, 255, 270, 285, 300, 310, 315, 325, 340, 355, 370, 385, 400.

NICORETTE® Freshfruit Chewing Gum 2 mg and 4mg: blister packs of 15, 30, 75,105, 150, 180, 200, 210, 225, 240, 255, 270, 285, 300, 310, 315, 325, 340, 355, 370, 385, 400.

NICORETTE® Icy Mint Chewing Gum 2 mg and 4mg: blister packs of 15, 30, 75, 105, 150, 180, 200, 210, 225, 240, 255, 270, 285, 300, 310, 315, 325, 340, 355, 370, 385, 400 and carton packs of 25, 100.

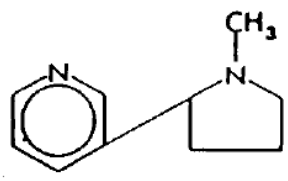
NICORETTE® Spearmint Chewing Gum 2 mg and 4mg: blister packs of 15, 30, 75, 105, 120, 150, 165, 180, 195, 200, 210, 225, 240, 300, 310, 315, 325, 340, 355, 370, 385, 400.

(not all flavours and pack sizes are 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 PHYSICOCHEMICAL PROPERTIES
The chemical name for nicotine is (S)-3-(1-methyl-2-pyrrolidinyl)pyridine.

The chemical structure is:



CAS 54-11-5

7 MEDICINE SCHEDULE (POISONS STANDARD)
Unscheduled

8 SPONSOR
Johnson & Johnson Pacific
45 Jones Street
Ultimo NSW 2007
Australia

® Registered trademark

9 DATE OF FIRST APPROVAL
NICORETTE® Classic Chewing Gum 2 mg and 4 mg: 13 August 1991

NICORETTE® Freshmint Chewing Gum 2 mg and 4 mg: 06 December 2004

NICORETTE® Freshfruit Chewing Gum 2 mg and 4 mg: 24 July 2007

NICORETTE® Icy Mint Chewing Gum 2 mg and 4 mg: 07 October 2009

NICORETTE® Spearmint Chewing Gum 2 mg and 4 mg: 06 February 2020

10 DATE OF REVISION
Date of revision: 28 April 2023

Summary table of changes

Section changed	Summary of new information
All	Update to new PI format. Addition of pack sizes to section 6.5. Addition of more restrictive safety related statements to section 4.8.
2, 3, 5.3, 6.1, 6.5	Reformatting of PI to the TGA's format and addition of more restrictive safety related statements to section. Addition of information relating to new Spearmint variant. Correction of colour description for Freshfruit gum.
4.4, 4.8, 6.5	Addition of safety-related information on epilepsy and seizures, inclusion of additional pack sizes.