NEW ZEALAND DATA SHEET

1 PRODUCT NAME

Nicorette® Gum, Nicorette® Freshmint Gum, Nicorette® Freshfruit Gum, Nicorette® Spearmint Gum and Nicorette® Icy Mint Gum

Chewing Gum containing 2mg or 4mg 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

For the treatment of tobacco dependence by relieving nicotine craving and withdrawal symptoms thus:

Facilitating smoking cessation in smokers motivated to quit.

Helping smokers to temporarily abstain from smoking.

Facilitating smoking reduction in smokers unable or unwilling to quit.

4.2 Dose and method of administration

Could be used as a single treatment or in combination with nicotine patch.

Each piece of Nicorette gum should be chewed intermittently for about 30 minutes. Nicorette gum should be chewed until a strong taste or a slight tingling sensation is felt, then stop chewing, place the gum between the cheek and gums until the taste or tingling has disappeared, then chew slowly again and repeat.

Children and Adolescents

Nicorette chewing gum should not be administered to persons under 18 years of age without recommendation from a health care professional. There is limited experience of treating this age group with Nicorette chewing gum.

Adults and Elderly

For single use

Use the gum whenever there is an urge to smoke. The initial dosage should be individualised on the basis of the patient's nicotine dependence. 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. Low dependent smokers (Fagerström Test for Nicotine Dependence (FTND) < 6 or smoking ≤ 20 cigarettes/day) should begin treatment with the 2mg strength and high dependent smokers should receive the 4 mg dosage, initially.

Smoking cessation

Use the gum 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.

Smoking reduction

Use the gum between smoking episodes whenever there is an urge to smoke, to prolong smoke-free intervals and with the intention to reduce your smoking as much as possible. If a reduction in number of cigarettes per day has not been achieved after 6 weeks it should be considered to seek professional advice.

A quit attempt should be made as soon as you feel ready but not later than 6 months after start of treatment. If it is not possible to make a serious quit attempt within 9 months after start of treatment then seek professional advice.

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. Any spare gum should be retained, as craving may suddenly occur.

Advice and support normally improve the success rate.

Temporary abstinence

Use the gum during smoke-free periods, for example in smoke-free areas or in other situations when you wish to avoid smoking, and there is an urge to smoke.

In combination with nicotine patch

Persons who have failed with single treatment or want to reduce the daily intake of the chewing gum because of local adverse events, can use NICORETTE® 16hr INVISIPATCH® patches in addition to the 2mg chewing gum.

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 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® 4mg Gum.

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.

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. After removal, the patch should be folded in half, adhesive side innermost, and placed inside the opened sachet., or in a piece of aluminium foil. The used patch should then be disposed of carefully, away from the reach of children or animals. Suspected nicotine poisoning in a child should be considered a medical emergency and treated immediately.

Underlying cardiovascular disease

In stable cardiovascular disease NICORETTE® 16hr INVISIPATCH® patch 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® 16hr INVISIPATCH® patch 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.

Generalised dermatological disorders

Patients with chronic generalised dermatological disorders such as psoriasis, chronic dermatitis or urticaria should not use NICORETTE® 16hr INVISIPATCH® patch.

Erythema may occur. If it is severe or persistent, treatment should be discontinued.

Phaeochromocytoma and uncontrolled hyperthyroidism

Nicotine, from both NRT and smoking, causes the release of catecholamines from the adrenal medulla. Therefore, NICORETTE® 16hr INVISIPATCH® patch 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.

Continued smoking while using NRT

Patients must be made aware that should they continue to smoke whilst using NICORETTE® 16hr INVISIPATCH® patch they may experience increased adverse effects due to the increased levels of nicotine beyond those normally experienced with smoking alone. Such adverse effects include cardiovascular effects (eg. angina, rapid or irregular heart beats).

Use in hepatic impairment

NICORETTE® 16hr INVISIPATCH® patch 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® 16hr INVISIPATCH® patch 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® 16hr INVISIPATCH® patch 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.

Effects on laboratory test

No data available.

4.5 Interaction with other medicines and other forms of interaction

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.

Smoking (but not nicotine) is associated with increase in CYP1A2 activity. After cessation of smoking, reduced clearance of substrates for this enzyme may occur. This may lead to an increase in plasma levels for some medicinal products of potential clinical importance for products with a narrow therapeutic window, e.g. theophylline, tacrine, clozapine and ropinirole.

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

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

4.6 Fertility, pregnancy and lactation

Studies have shown a decrease of litter size in rats treated with nicotine during the time of fertilisation.

Use in pregnancy

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 medicated chewing gum, has no or negligible influence on the ability to drive and use machines.

4.8 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 iation*
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**
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 authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

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 advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drug for treatment of nicotine dependence.

ATC code: N07B A01.

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 or reduce their smoking.

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 is dibasic with a pKa1 of approximately 3 and a pKa2 around 8. Thus, nicotine is a weak base and its movement across cell membrane is pH dependent. It is easily soluble in both water and lipids depending on the degree of ionization. There are two stereoisomers of nicotine, (S)- and (R)-form, but it is only (S)-nicotine that is biologically active.

The pharmacokinetic studies of nicotine products have been performed in adult smokers. There are no differences in nicotine kinetics between men and women.

The bioavailability of nicotine administered with Classic Gum 2 mg is 65% and Mint Gum 4 mg is 54%.

Absorption
The major part of nicotine released from chewing gums is absorbed through the oral mucous membranes.

In a PK study with the 2 mg gum (including 17 subjects) demonstrable plasma concentrations of nicotine were obtained within 5-7 minutes after start of chewing and reached a maximum at the end of chewing (i.e. after 30 minutes of chewing, using a metronome to control the chewing rate) or shortly thereafter. The amount of nicotine extracted from one chewing gum depends on how vigorously and for how long it is chewed. After 30 minutes of chewing at a rate of one chew every two seconds, the mean amounts of nicotine extracted from the 2 mg gum have ranged

between 1.3 and 1.6 mg in PK studies, and between 2.5 and 3.5 mg from the 4 mg gum. The amount of nicotine absorbed depends on the proportion of the dose extracted from the gum and the proportion lost due to swallowing and subsequent first-pass elimination in the liver.

Distribution
The volume of distribution following intravenous administration of nicotine, has been investigated in numerous studies. In six studies, mean values ranges between 2.2 and 3.3 L/kg.

Plasma protein binding of nicotine is considered to be low, about 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 the nicotine pharmacokinetics.

Metabolism
Results of pharmacokinetic studies suggest that nicotine metabolism and elimination are independent of the choice of nicotine formulation, and thus results from studies with intravenous administration of nicotine are used to describe distribution, biotransformation, metabolism and excretion.

The major eliminating organ is the liver, although the lungs and brain also metabolise nicotine to a small extent. The enzyme primarily involved in biotransformation of nicotine is CYP2 A6. Seventeen 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 terminal half-life of 14 to 20 hours; the plasma concentrations of cotinine exceed those of nicotine 10-fold.

Excretion
Mean values of total clearance of nicotine between 66.6 and 90.0 L/h have been reported and the elimination half-life averages about 2-3 hours.
The primary urinary metabolites of nicotine are cotinine and trans-3-hydroxycotinine. On average 10-12% of the absorbed nicotine dose is excreted as cotinine and 28-37% of the dose is excreted as trans-3-hydroxy-cotinine. About 10-15% of nicotine is excreted unchanged in the urine. However, with low urine pH (below 5), as much as 23% of the nicotine dose was excreted unchanged.

Mean AUC_{∞} of 14.7 and 28.2 ng/mLxh have been achieved following administration of gum 2 and 4 mg, respectively.

Progressive severity of renal impairment is associated with decreased total clearance of nicotine. Nicotine clearance was decreased by 50% on average in subjects with severe renal impairment. Raised nicotine levels have been seen in smoking subjects undergoing hemodialysis.

In smokers with liver cirrhosis but only mild impairment of hepatic function (Child-Pugh score 5), the pharmacokinetics of nicotine is unaffected. However, in smokers with moderately impaired liver function (Child-Pugh score 7), total clearance has

been reported to be reduced on average by 40-50%. There is no data about pharmacokinetics of nicotine in smokers with a Child-Pugh score exceeding 7.

Total clearance of nicotine is reduced in healthy elderly subjects, but deviations are variable and not considered sufficiently important to justify general age-dependent dose adjustments.

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 anhydrous, 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 anhydrous, acesulfame potassium, levomenthol, 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 anhydrous, acesulfame potassium, levomenthol, 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 anhydrous, acesulfame potassium, levomenthol, 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 anhydrous, acesulfame potassium, levomenthol, 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 Gum 30 months

NICORETTE® Freshmint Gum 36 months

NICORETTE® Freshfruit Gum 36 months

NICORETTE® Spearmint Gum 36 months

NICORETTE® Icy Mint Gum 36 months

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

NICORETTE® Classic Gum 2mg and 4mg: 15, 30 and 105 pieces

NICORETTE® Freshmint Gum 2mg and 4mg: 15, 30 and 105 pieces

NICORETTE® Freshfruit Gum 2mg and 4mg: 15, 30, 60 and 105 pieces

NICORETTE® Spearmint Gum 2mg and 4mg: 15, 30, 75, 105, 120, 150, 165, 180, 195, 210, 225 and 240 pieces

NICORETTE® Icy Mint Gum 2mg and 4mg: 15, 30, 105 and 210 pieces

(not all pack sizes are marketed)

The chewing gums are packed in press through packages (blister packages) held together within a cardboard box.

6.6 Special precautions for disposal

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

7 MEDICINE SCHEDULE

General Sales Medicine

8 SPONSOR

Johnson & Johnson (New Zealand) Ltd
507 Mt. Wellington Highway
Mt. Wellington, Auckland 1060

P.O. Box 62-185, Sylvia Park
Auckland 1644

9 DATE OF FIRST APPROVAL

2 October 2014

10 DATE OF REVISION OF THE TEXT

06 December 2019

Summary table of changes

Section changed	Summary of new information
All	Update to new PI format. Addition of information relating to new Spearmint variant. Addition of more restrictive safety and related statements. Updates to Adverse event data.