SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Nicorette Pepparmint 2 mg medicated chewing gum
Nicorette Pepparmint 4 mg medicated chewing gum

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

2 mg: Nicotine resinate 10 mg, equivalent to nicotine 2 mg
4 mg: Nicotine resinate 20 mg, equivalent to nicotine 4 mg

Excipient with known effect:
Butylated hydroxytoluene (E321), less than 0,6 mg/chewing gum.
2 mg: Xylitol 608 mg/chewing gum.
4 mg: Xylitol 596 mg/chewing gum.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Medicated chewing gum

2 mg: whitish, coated chewing gum, approximately 15 x 15 x 6 mm
4 mg: cream-coloured, coated chewing gum, approximately 15 x 15 x 6 mm

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For treatment of tobacco dependence by alleviating nicotine craving and withdrawal symptoms and thus assisting smoking cessation in smokers who are motivated to quit or to alleviate smoking reduction in smokers who are unable or unwilling to quit smoking.

Nicorette Pepparmint chewing gum should preferably be used in conjunction with a smoking cessation program.

4.2 Posology and method of administration

Chewing gum 2 mg: can be used as a single treatment or in combination with Nicorette transdermal patch.
Chewing gum 4 mg: to be used as a single treatment.

The user should not eat or drink with chewing gum in the mouth. Beverages that lower the pH in the oral cavity, e.g. coffee, juice and soft drinks, may reduce absorption of nicotine in the oral cavity. To achieve maximum absorption of nicotine these beverages should be avoided for up to 15 minutes before the chewing gum is used.

Administration of nicotine should be stopped temporarily if any symptoms of nicotine excess occur. Nicotine intake should be decreased by either lowering dosing frequency or strength if nicotine excess symptoms persist (see section 4.9).

Paediatric population
Nicorette Pepparmint chewing gum should not be used by adolescents (12-17 years) without recommendation from a healthcare professional.

Nicorette Pepparmint chewing gum should not be used by children under the age of 12 years.

Adults and the elderly

Nicorette Pepparmint chewing gum for single use
Each piece of Nicorette Pepparmint chewing gum should be chewed slowly for approx. 30 minutes, with pauses. Nicorette Pepparmint should be chewed until a strong taste or a mildly burning sensation is experienced: then stop chewing, let the chewing gum rest between the cheek and the gums until the taste and the burning sensation have disappeared, then chew again slowly and repeat.

The strength of the chewing gum should be chosen on the basis of the patient's nicotine dependence. For a low level of dependence, 2 mg chewing gum should be used. For a high level of dependence (FTND $\geq$ 6 or smokes > 20 cigarettes/day) or after previous failure with the 2 mg chewing gum 4 mg should be used.

Abrupt cessation of smoking:

Nicorette should be used when cigarettes normally would have been smoked or if cravings emerge.
At the start of treatment 1 piece of chewing gum may be taken every other hour. Sufficient chewing gums should be used each day. The dosage should be individualised on the basis of the smoker´s nicotine dependence. In most cases 8-12 pieces of chewing gum per day, irrespective of strength, is sufficient. In order to maximize the chances of success it is important not to underdose. No more than 24 pieces of chewing gum per day should be taken.

The period of treatment is individual. Normally treatment should continue for at least 3 months. The dose of nicotine is then reduced gradually. Treatment should be terminated when the dose has decreased to 1-2 pieces of chewing gum per day. Regular use of Nicorette Pepparmint chewing gums beyond 12 months is generally not recommended, although some former ex-smokers may require prolonged treatment in order to avoid relapse to smoking. Spare chewing gums should be retained in the event of sudden cravings.

Gradual cessation through progressive reduction in smoking:

Nicorette Pepparmint chewing gum is used between smoking periods to prolong smoke free intervals and with the aim to reduce smoking as much as possible. If a reduction in number of cigarettes per day has not been reached after 6 weeks, professional help should be sought.

Attempts to stop smoking should be done as soon as the smoker feels ready, however, not later than 6 months after beginning of treatment. When the number of cigarettes has been

reduced to a level from which the user feels able to quit completely, then the schedule for "abrupt cessation" as given above should be started. If it is not possible to make a serious attempt within 9 months after beginning of treatment, professional help should be sought. Regular use of Nicorette Pepparmint chewing gums beyond 12 months is generally not recommended, although some former ex-smokers may require prolonged treatment in order to avoid relapse to smoking. Spare chewing gums should be retained in the event of sudden cravings.

Treatment with Nicorette Pepparmint 2 mg chewing gum in combination with Nicorette transdermal patch

Highly dependent smokers, those who experience cravings despite use of nicotine medicine or those who have failed with single treatment with nicotine medicine can use Nicorette transdermal patch together with Nicorette Pepparmint 2 mg chewing gum for fast relief of smoke cravings.

Initial combination treatment

The treatment should begin with one 25 mg/16 hours patch daily combined with Nicorette Pepparmint 2 mg chewing gum. Nicorette Pepparmint 2 mg chewing gum is used as required for fast relief of craving (usually 5-6 chewing gums per day). A maximum of 24 chewing gums per day should be used. Smokers should stop smoking completely during the combination treatment. Normally, the treatment continues for 8 weeks.

The patch is applied in the morning and removed at bedtime. The patch is applied on a clean, dry, hairless and uninjured area of skin on the trunk, arms or hips.

To reduce the risk of local irritation the Nicorette transdermal patches should be applied alternately at different sites.

The hands should be washed carefully after applying the transdermal patch to avoid irritation of the eyes with nicotine from the fingers.

Weaning from nicotine medicine:

After the initial 8 weeks gradual weaning from nicotine medicine is started by either

- using a patch with a lower strength, i.e. 15 mg/16 hours during 2 weeks followed by 10 mg/16 hours for additional 2 weeks in combination with the initial dose of Nicorette Pepparmint 2 mg chewing gums. Thereafter gradually reduce the number of chewing gums up to 12 months.

or

- stop using the patch and gradually reduce the number of chewing gums up to 12 months.

Recommended dosage in tabular format:

Time period	**Patch**	**Chewing gum 2 mg**
Week 1-8	1 patch 25 mg/16 hours per day	As needed.

		Usual dose is 5-6 chewing gums per day (max 24)
Weaning from nicotine medicine - alternative 1		
Week 9-10	1 patch 15 mg/16 hours per day	Continue to use chewing gums as needed.
Week 11-12	1 patch 10 mg/16 hours per day	Continue to use chewing gums as needed.
Up to 12 months	---	Reduce the number of chewing gums gradually.
Weaning from nicotine medicine – alternative 2		
Up to 12 months	---	Continue to reduce the number of chewing gums gradually.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Children under the age of 12 years.
- Non-smokers.

4.4 Special warnings and special precautions for use

The benefits of quitting smoking outweigh any risks associated with correctly administered nicotine medicine.
A risk-benefit assessment should be made by an appropriate healthcare professional for patients with the following conditions:

- *Cardiovascular disease:* Dependent smokers with a recent myocardial infarction, unstable or worsening angina including Prinzmetal's angina, severe cardiac arrhythmias, recent cerebrovascular accident and/or who suffer with uncontrolled hypertension should be encouraged to stop smoking with non-pharmacological interventions (such as counselling). If this fails, Nicorette Pepparmint chewing gum may be considered but as data on safety in this patient group are limited, initiation should only be under close medical supervision.

- *Diabetes Mellitus.* Patients with diabetes mellitus should be advised to monitor their blood sugar levels more closely than usual when smoking is stopped and nicotine medicine is initiated as reduction in nicotine induced catecholamine release can affect carbohydrate metabolism. They may need lower doses of insulin as a result of smoking cessation.

- *Renal and hepatic impairment:* Use with caution in patients with moderate to severe hepatic impairment and/or severe renal impairment as the clearance of nicotine or its metabolites may be decreased with the potential for increased adverse effects.

- *Phaeochromocytoma and uncontrolled hyperthyroidism:* Nicotine, both from nicotine medicine and from smoking, causes release of catecholamines from the adrenal medulla. Therefore Nicorette Pepparmint chewing gum should be used with caution by patients with uncontrolled hyperthyroidism or phaeochromocytoma.

- *Gastrointestinal Disease:* Nicotine may exacerbate symptoms in patients suffering from esophagitis, gastric or peptic ulcers and nicotine medicine should be used with caution in these conditions.
- *Seizures*: Use with caution in subjects taking anti-convulsant therapy or with a history of epilepsy as cases of convulsions have been reported in association with nicotine (see section 4.8).

Smokers who wear dentures may experience difficulty in chewing Nicorette Pepparmint. The chewing gum may adhere to and, in rare cases, damage dental plates and bridges.

Danger in children: Doses of nicotine tolerated by smokers can produce severe toxicity in children that may be fatal. Products containing nicotine should not be left where they may be handled or ingested by children see section 4.9 Overdose.

Transferred dependence: Transferred dependence with Nicorette Pepparmint chewing gum is rare and both less harmful than tobacco and easier to break than smoking dependence.

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, tacrine, clozapine and ropinirole. The plasma concentration of other medicinal products metabolised in part by CYP 1A2 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.

Excipients:
Nicorette Pepparmint contains xylitol, which may have a laxative effect.
Calorie content: 2.4 kcal/g xylitol, which corresponds to 1.5 kcal and 1.4 kcal, respectively, per chewing gum (Nicorette Pepparmint 2 mg and 4 mg, respectively).
The chewing gum base contains butylated hydroxytoluene (E321), an anti-oxidant, which may cause local skin reactions (e.g. contact dermatitis) or irritation to the eyes and mucous membranes.
This medicine contains less than 1 mmol sodium (23 mg) per chewing gum, i.e. is essentially ‘sodium- free’.

Special warnings and precautions for the combination of Nicorette Pepparmint chewing gum and Nicorette transdermal patch are the same as those for each treatment alone (see Summary of Product Characteristics for Nicorette transdermal patch).

4.5 Interaction with other medicinal products and other forms of interaction

No clinically relevant interactions between nicotine medicines 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 increased pain response (angina-pectoris type chest pain) provoked by adenosine administration (see section 4.4, Stopping smoking).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/ contraception in males and females
In contrast to the well-known adverse effects of tobacco smoking on human conception and pregnancy, the effects of therapeutic nicotine treatment are unknown. Thus, whilst to date no specific advice regarding the need for female contraception has been found to be necessary, the most prudent state for women intending to become pregnant to be in is to be both non-smoking, and not using nicotine medicine.

Whilst smoking may have adverse effects on male fertility, no evidence exists that particular contraceptive measures are required during nicotine medicine treatment by males.

Pregnancy
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.
Nicotine passes over to the foetus and influences the foetal breathing pattern and circulation. The effect on the foetal circulation is dose-dependent. Pregnant smokers should therefore always be recommended to stop smoking completely without the use of nicotine medicine. The risk of continued smoking may however constitute a greater hazard to the foetus than use of nicotine medicine in a supervised smoking cessation programme. Nicorette Pepparmint chewing gum should only be used by pregnant patients with a high level of nicotine dependence after advice from a healthcare professional.

Lactation
Nicotine passes over in breast milk in such quantities that may affect the child even at therapeutic doses. Nicorette Pepparmint should therefore be avoided during breastfeeding. Should smoking cessation not be achieved, use of Nicorette Pepparmint by breast feeding smokers should only be initiated after advice from a healthcare professional. Women should then take the chewing gum just after breastfeeding.

Fertility
Smoking increases the risk for infertility in women and men. *In vitro* studies have shown that nicotine can adversely affect human sperm quality. In rats, impaired sperm quality and reduced fertility has been shown.

4.7 Effects on ability to drive and use machines

Nicorette Pepparmint has no or negligible effect on ability to drive cars or use machines.

4.8 Undesirable effects

Effects of smoking cessation
Regardless of the means used, a variety of symptoms are known to be associated with quitting habitual tobacco use. These include emotional or cognitive effects such as dysphoria or depressed mood; insomnia; irritability, frustration or anger; anxiety; difficulty concentrating, and restlessness or impatience. There may also be physical effects such as decreased heart rate; increased appetite or weight gain, dizziness or presyncopal symptoms, cough, constipation, gingival bleeding or apthous ulceration, or nasopharyngitis. In addition, and of clinical significance, nicotine cravings may result in profound urges to smoke.

Adverse Drug Reactions
Nicorette Pepparmint chewing gum may cause side effects resembling those that occur when nicotine is administered by a different route. Most side effects that have been reported by patients usually appear during the first 3-4 weeks after the start of treatment. The side effects of nicotine chewing gums are largely due to incorrect chewing technique or to the pharmacological effects of nicotine, which are dose-dependent.

Irritation in the mouth and throat may be experienced, however most subjects adapt to this with ongoing use.

Allergic reactions (including symptoms of anaphylaxis) rarely occur with the use of Nicorette Pepparmint.
The adverse reactions observed in patients treated with oral nicotine formulations during clinical trials and post-marketing experience are listed below by system organ class.
The frequency categories have been estimated from clinical trials for the adverse reactions identified during post-marketing experience.

Very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1 000, <1/100); rare (≥1/10 000, <1/1 000); very rare (<1/10 000), not known (cannot be estimated from the available data).

System Organ Class	**Reported adverse event**
Immune System Disorders	
Common	Hypersensitivity
Not known	Anaphylactic reaction
Psychiatric Disorders	
Uncommon	Abnormal dreams
Nervous system disorders	
Very common	Headache
Common	Dysgeusia, Paraesthesia
Not known	Seizure*
Eye disorders	
Not known	Blurred Vision, Lacrimation increased
Cardiac disorders	
Uncommon	Palpitations, Tachycardia
Rare	Atrial fibrillation
Vascular Disorders	
Uncommon	Flushing, Hypertension

Respiratory, Thoracic and Mediastinal Disorders	
Very common	Cough, Hiccups, Throat irritation
Uncommon	Bronchospasm, Dysphonia, Dyspnoea, Nasal Congestion, Oropharyngeal pain, Sneezing, Throat tightness
Skin and subcutaneous tissue disorders	
Uncommon	Urticaria, Hyperhidrosis, Pruritus, Rash
Not known	Angioedema, Erythema
Musculoskeletal and connective tissue disorders	
Uncommon	Jaw-muscle ache
Not known	Tightness of jaw
Gastrointestinal disorders	
Very common	Nausea
Common	Vomiting, Abdominal pain, Flatulence, Diarrhoea, Dry mouth, Dyspepsia, Salivary hypersecretion, Stomatitis
Uncommon	Eructation, Glossitis, Oral mucosal blistering and exfoliation, Paraesthesia oral
Rare	Dysphagia, Hypoaesthesia oral, Retching
Not known	Dry throat, Gastrointestinal discomfort, Lip pain
General disorders and administration site conditions	
Common	Burning sensation, Fatigue
Uncommon	Asthenia, Chest discomfort and pain, Malaise

*Cases of seizures have been reported in subjects taking anti-convulsant therapy or with a history of epilepsy.

Adverse events that may occur when using the combination treatment (chewing gum and patch) only differ from each treatment alone in terms of local adverse events associated with the pharmaceutical form. The frequencies of these adverse events are comparable to those reported in the Summary of Product Characteristics for respectively product.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 to (see details below).

Medical Products Agency
Box 26
751 03 Uppsala
Website: www.lakemedelsverket.se

4.9 Overdose

Symptoms of overdosage with nicotine may occur if the patient has low nicotine consumption before treatment or uses other concomitant sources of nicotine.

The symptoms of overdosage are the same as the symptoms of acute nicotine poisoning, such as nausea, vomiting, increased salivation, abdominal pain, diarrhoea, sweating, headache, dizziness, disturbed hearing and a pronounced feeling of weakness. At high doses these

symptoms may be accompanied by low blood pressure, weak and irregular pulse, breathing difficulties, exhaustion, circulatory collapse and general convulsions.

Nicotine doses that are tolerated by adult smokers during treatment may cause serious symptoms of poisoning in children that may have a fatal outcome. Suspected nicotine poisoning in a child should be considered a medical emergency and treated immediately.

*Management of overdose***:** Administration of nicotine must be stopped immediately and the patient should be treated symptomatically. If excessive amount of nicotine is swallowed, activated charcoal reduces the gastrointestinal absorption of nicotine.

The acute minimum lethal oral dose of nicotine in man is believed to be 40 to 60 mg.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Agent for nicotine dependence.
ATC code: N07BA01

Abruptly interrupted use of tobacco products after a long period of daily use may give characteristic withdrawal symptoms comprising four or more of the following: dysphoria or depressed mood, insomnia, irritability, frustration or aggression, anxiety, difficulty in concentrating, restlessness or impatience, reduced heart rate, increased appetite or increase in weight. Urge to smoke, recognized as a clinically relevant symptom, is an important part of the withdrawal symptoms when giving up smoking.

Clinical studies have shown that nicotine medications may help smokers to refrain from smoking.

Comparative studies of effects between different forms of preparation of Nicorette have not been carried out.

5.2 Pharmacokinetic properties

The quantity of released nicotine that is absorbed from nicotine chewing gum depends on the quantity of nicotine released in the oral cavity and how much disappears as a result of swallowing. Most of the nicotine that is released is absorbed through the oral mucosa. The systemic bioavailability of swallowed nicotine is lower owing to first-pass elimination. The high and rapidly rising concentrations of nicotine that are seen from smoking are seldom reached during treatment with chewing gum.

Normally approx. 1.4 mg of nicotine is released from a 2 mg piece of chewing gum and approx. 3.4 mg of nicotine from a 4 mg piece. Maximum blood concentration is reached after 30 minutes' chewing and is then comparable with the concentration 20-30 minutes after smoking a medium-strength cigarette.

The volume of distribution after intravenous administration of nicotine is around (2-)3 l/kg and the half-life is approx. 2 hours. Nicotine is metabolized largely in the liver and plasma

clearance is on average around 70 l/hour. Nicotine is also metabolized in kidneys and lungs. More than 20 metabolites have been identified, of which all are believed to be less active than nicotine. The main metabolite is cotinine, which has a half-life of 15-20 hours and which gives approx. 10 times as high a plasma concentration as nicotine. The plasma protein binding of nicotine is less than 5%.

Other diseases or concomitant use of other medicinal products that affect the level of plasma proteins are not expected to have a significant effect on the nicotine kinetics. The main metabolites in urine are cotinine (15% of the dose) and trans-3-hydroxy cotinine (45% of the dose). Approx. 10% of the nicotine is excreted unchanged with the urine. Up to 30% may be excreted with the urine via increased diuresis and acidification below pH 5.

Greatly impaired renal function is assumed to affect total clearance of nicotine. The pharmacokinetics of nicotine is unaffected in liver cirrhosis patients with mild impairment of liver function (Child score 5) and reduced in liver cirrhosis patients with moderate impairment of liver function (Child score 7). Elevated nicotine levels have been seen in smoking haemodialysis patients.

A smaller reduction in total clearance of nicotine has been shown in healthy elderly users, but adjustment of the dose is not necessary.

No differences in nicotine kinetics have been observed between men and women.

5.3 Preclinical safety data

There are no preclinical safety data for nicotine chewing gum.

As a component of tobacco, however, the toxicity of nicotine is well documented. The most common symptoms of an overdose of nicotine are nausea and vomiting. The symptoms of acute poisoning are weak and irregular pulse, breathing difficulties and general convulsions.

There is no evidence that nicotine would be genotoxic or mutagenic. The well-known carcinogenic properties of tobacco smoke are formed mainly during pyrolysis of tobacco. This does not occur with nicotine chewing gum.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

2 mg

Chewing gum base (contains butylhydroxytoluene E321)
Xylitol 608 mg
Peppermint oil
Sodium carbonate, anhydr.
Sodium hydrogen carbonate
Acesulfame potassium
Levomenthol

4 mg

Chewing gum base (contains butylhydroxytoluene E321)
Xylitol 596 mg
Peppermint oil
Sodium carbonate, anhydr.
Acesulfame potassium
Levomenthol
Magnesium oxide, light

Magnesium oxide, light
Acacia
Titanium dioxide
Carnauba wax
Talc

Acacia
Titanium dioxide
Carnauba wax
Quinoline yellow (E104)
Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25ºC.

6.5 Nature and contents of container

2 mg: 10 pcs, 12 pcs, 15 pcs, 24 pcs, 30 pcs, 48 pcs, 90 pcs, 96 pcs, 105 pcs, 204 pcs and 210 pcs chewing gum in blister pack (blister of 12 or 15 pcs) and patient information leaflet in cardboard box.

4 mg: 12 pcs, 15 pcs, 24 pcs, 30 pcs, 48 pcs, 90 pcs, 96 pcs, 105 pcs, 204 pcs and 210 pcs chewing gum in blister pack (blister of 12 or 15 pcs) and patient information leaflet in cardboard box.

The blister pack consists of PVC/PVDC film and aluminium foil/vinyl acrylic lacquer.

Not all pack sizes may be marketed.

6.6 Instructions for use and handling, and disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

McNeil Sweden AB
Box 4007
169 04 Solna

8 MARKETING AUTHORISATION NUMBER

2 mg: 20036
4 mg: 20037

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

2004-10-04/2007-01-01

10 DATE OF REVISION OF THE TEXT

2023-08-23