Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Nicotinell Mint 2 mg compressed lozenge

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each piece oflozenge contains:

Active substance: 2 mg nicotine (corresponding to 6.144 mg nicotine bitartrate dihydrate).
Excipient(s) with known effect: aspartame (0.01 g) and maltitol (0.9 g).
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Compressed lozenge
White, mint flavoured, round biconvex lozenge

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of tobacco dependence by providing relief of nicotine withdrawal symptoms including cravings (see section 5.1), thereby facilitating smoking cessation or temporary smoking reduction in smokers motivated to quit smoking. Permanent cessation of tobacco use is the eventual objective.

The 2 mg strength is used when severe withdrawal symptoms are experienced.

Patient counsellingand support normally improve the success rate.

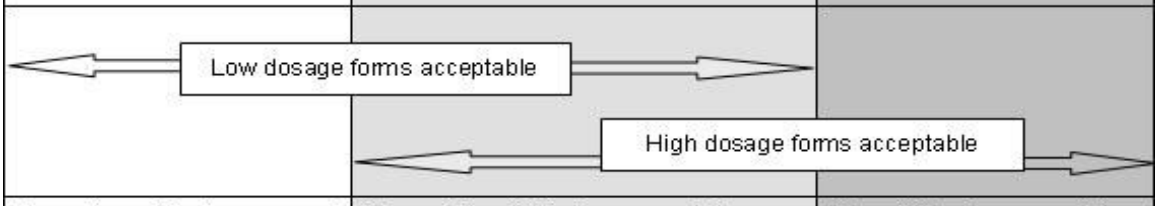
4.2 Posology and method of administration

Posology:

Adults and elderly

Nicotinell Mint 2 mg Lozenge is intended to be used by smokers with a strong or very strong nicotine dependency and those who have previously failed to stop smoking with the aid of nicotine replacement therapy.
The optimal strength is selected according to the following table:

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Low to moderate dependency	Moderate to strong dependency	Strong to very strong dependency
		
Less than 20 cigarettes / day	From 20 to 30 cigarettes / day	Over 30 cigarettes / day
Low dose forms are preferable (1 mg lozenge)	Low (1 mg lozenge) or high (2 mg lozenge) dose forms are acceptable depending on patient characteristics and preference.	High dose forms are preferable (2 mg lozenge)

If an adverse event occurs with the use of the high dose form (2 mg lozenge), use of the low dose form (1 mg lozenge) should be considered.

The initial dosage should be individualised on the basis of the patient's nicotine dependence. One piece of lozenge to suck when the user feels the urge to smoke.

Initially, 1 lozenge should be taken every 1-2 hours. The usual dosage is 8-12 lozenges per day. For smoking cessation and smoking reduction with Nicotinell Lozenge, the maximum daily dose is 15 lozenges. Do not use more than one lozenge per hour.

Nicotinell Lozenge should primarily be used for smoking cessation.

Smoking cessation:
Users should stop smoking completely during treatment with Nicotinell Lozenge.

The treatment duration is individual. Normally, treatment should continue for at least 3 months. After 3 months, the user should gradually reduce the number of lozenges or alternatively the user should switch to nicotine 1 mg lozenges and then gradually reduce the number of lozenges per day. Treatment should be discontinued when the dose has been reduced to 1-2 lozenges per day. Use of nicotine medicinal products like Nicotinell Mint 2 mg Lozenge beyond 6 months is generally not recommended. Some ex-smokers may need treatment with the lozenge longer to avoid returning to smoking.

Patients who have been using oral nicotine replacement therapy beyond 9 months are advised to seek additional help and information from health care professionals.

Counselling may help smokers to quit.

Smoking reduction:
Nicotinell Lozenge should be used between periods of smoking in order to prolong smoke-free intervals and with the intention of reducing smoking as much as possible. The number of cigarettes should be gradually replaced by Nicotinell Lozenge. If a reduction of at least 50 % in the number of cigarettes per day has not been achieved after 6 weeks, professional advice should be sought. A quit attempt should be made as soon as the smoker feels ready, but not later than 4 months after start of treatment. After that the number of lozenges should be gradually reduced, for example by quitting one lozenge every 2-5 days. If a quit attempt cannot be made within 6 months after starting treatment, professional advice should be sought. Regular use of Nicotinell Lozenge beyond 6 months is generally not recommended. Some ex-smokers may need treatment with the lozenges for longer to avoid returning to smoking.
Counselling may improve the chance for smokers to quit.

Paediatric population

Nicotinell Lozenge should not be used by adolescents 12-17 years of age without prescription from a healthcare professional. There is no experience in treating adolescents under the age of 18 with Nicotinell Lozenge.

Children below 12 years of age:
Nicotinell Lozenges should not be used by children under 12 years.

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

Method of administration:

1. One lozenge to be sucked until the taste becomes strong.
2. The lozenge should then be lodged between the gum and cheek.
3. When the taste fades, sucking of the lozenge should commence again.
4. The sucking routine will be adapted individually and should be repeated until the lozenge dissolves completely (about 30 minutes).

Concomitant use of acidic beverages such as coffee or soda may decrease the buccal absorption of nicotine. Acidic beverages should be avoided for 15 minutes prior to sucking the lozenge. Users should not eat or drink while a lozenge is in the mouth.

4.3 Contraindications

Hypersensitivity to nicotine or to any of the excipients listed in section 6.1.
Nicotinell Lozenge should not be used by non-smokers.

4.4 Special warnings and precautions for use

Cardiovascular disease: smokers with a recent myocardial infarction, unstable or worsening angina including Prinzmetal's angina, severe cardiac arrhythmias, uncontrolled hypertensions or recent cerebrovascular accident should be encouraged to stop smoking with non-pharmacological interventions (such as counselling). If this fails, Nicotinell Lozenges may be considered but as data on safety in this patient group are limited, initiation should only be under close medical supervision. If there is a clinically significant increase in cardiovascular or other effects attributable to nicotine, the nicotine lozenge dose should be reduced or discontinued.

Nicotinell Lozenges should be used with caution in patients with hypertension, stable angina pectoris, cerebrovascular disease, occlusive peripheral arterial disease, heart failure, hyperthyroidism or pheochromocytoma.
Diabetes mellitus: blood glucose levels may be more variable during smoking cessation, with or without nicotine replacement therapy. So, it is important for diabetics to closely monitor their blood glucose levels while using this product.

Renal or hepatic impairment: moderate to severe hepatic and/or severe renal impairment.

Seizures: potential risks and benefits of nicotine should be carefully evaluated before use in subjects taking anti-convulsant therapy or with a history of epilepsy as cases of convulsions have been reported in association with nicotine.

Patients should initially be encouraged to stop smoking with non-pharmacological interventions (such as counselling).

Gastrointestinal disease: swallowed nicotine may exacerbate symptoms in subjectssuffering from active oesophagitis, oral and pharyngeal inflammation, gastritis or peptic ulcer.

Nicotine oral products should be kept out of sight and reach of children.

Danger in small children: doses of nicotine that are tolerated by adult smokers during treatment may produce severe symptoms of poisoning in small children and may prove fatal (please see Section 4.9).

Special warnings about excipients

Nicotinell Mint Lozenges contains aspartame, maltitol and sodium.

Each Nicotinell Mint 2 mg Lozenge contains 10 mg aspartame (E951), a source of phenylalanine equivalent to 5 mg/dose and may be harmful for people with phenylketonuria.

Because Nicotinell Mint 2 mg Lozenge contains maltitol (E965), a source of fructose:
- patients with rare hereditary problems of fructose intolerance should not take this medicinal product,
- patients may experience a mild laxative effect.

Calorific value 2.3 kcal/g maltitol.

This medicinal product contains less than 1 mmol (23 mg) per lozenge that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Drug Interactions: No information is available on interactions between Nicotinell Lozenge and other medicinal products.

Smoking Cessation: Smoking but not nicotine is associated with increased CYP1A2 activity. After stopping smoking there may be reduced clearance of substrates for this enzyme and increased plasma levels of some medicinal products of potential clinical importance because of their narrow therapeutic window e.g. theophylline, tacrine, olanzapine and clozapine.

The plasma concentrations of other active substances metabolised by CYP1A2 e.g. caffeine, paracetamol, phenazone, phenylbutazone, pentazocine, lidocaine, benzodiazepines, warfarin, oestrogen and vitamin B12 may also increase. However, the clinical significance of this effect for these active substances is unknown.

Smoking may lead to reduced analgesic effects of propoxyphene, reduced diuretic response to furosemide (frusemide), reduced effect of propranolol on blood pressure and heart rate and reduced responder rates in ulcer healing with H2-antagonists.

Smoking and nicotine may raise the blood levels of cortisol and catecholamines, i.e. may lead to a reduced effect of nifedipine or adrenergic antagonists and to an increased effect of adrenergic agonists.

Increased subcutaneous absorption of insulin which occurs upon smoking cessation may necessitate a reduction in insulin dose.

4.6 Fertility, pregnancy and lactation

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 the pregnant smoker and her baby. The earlier abstinence is achieved the better. Nicotine passes to the foetus and affects its breathing movements and circulation. The effect on the circulation is dose-dependent.
Women who are pregnant should first be advised to stop smoking without the assistance of nicotine replacement therapy. If this fails, the use of nicotine replacement therapy should only be used after advice from a healthcare professional.

Breast-feeding
Nicotine is excreted in breast milk in quantities that may affect the child even in therapeutic doses. The lozenge, like smoking itself, should therefore be avoided during breast-feeding. Should smoking withdrawal not be achieved, use of the lozenge by breast feeding smokers should only be initiated after advice from a healthcare professional. Where nicotine replacement therapy is used whilst breast-feeding, the lozenge should be taken just after breast-feeding and not during the two hours before breast-feeding.

Fertility

Smoking increases the risk for infertility in women and men. Both in humans and in animals it has been shown that nicotine can adversely affect sperm quality. In animals, reduced fertility has been shown.

4.7 Effects on ability to drive and use machines

There is no evidence of any risks associated with driving or operating machinery when the lozenge is used following the recommended dose. Nevertheless one should take into consideration that smoking cessation can cause behavioural changes.

4.8 Undesirable effects

Nicotinell Lozenge can cause adverse reactions similar to those associated with nicotine administered by smoking. These can be attributed to the pharmacological effects of nicotine, which are dose-dependent. Non dose-dependent adverse reactions are as follows: hypersensitivity, angioneurotic oedema and anaphylactic reactions.

Most of the adverse reactions which are reported by patients occur generally during the first 3-4 weeks after initiation of therapy.

Nicotine from lozenges may sometimes cause a slight irritation of the throat and increased salivation at the start of the treatment. Excessive swallowing of nicotine which is released in the saliva may, at first, cause hiccups. Those who are prone to indigestion may suffer initially from minor degrees of dyspepsia or heartburn; slower sucking will usually overcome this problem.

Excessive consumption of lozenges by subjects who have not been in the habit of inhaling tobacco smoke, could possibly lead to nausea, faintness and headache.

Increased frequency of aphthous ulcer may occur after abstinence from smoking.

The following undesirable effects detailed in Table 1 are nicotine related adverse events for all oral dosage forms.

Adverse reactions are listed below, by system organ class and frequency. Frequencies are defined as: *very common* (≥1/10), *common* (≥1/100 to <1/10), *uncommon* (≥1/1,000 to <1/100), *rare* (≥1/10,000, <1/1,000) or *very rare* (<1/10,000).

Table 1 shows events which were identified from a double-blind, randomised, placebo-controlled lozenge clinical study involving 1818 patients. Adverse events reported in this study have been considered for inclusion, where the incidence in the 2 mg or 4 mg nicotine arm was higher than the corresponding placebo arm. Frequencies are calculated from safety data of the study.

Table 1: Adverse Reactions from clinical trial data

System Organ Class	**Very Common** (≥1/10)	**Common** (≥1/100 to <1/10)	**Uncommon** (≥1/1,000 to <1/100)	**Rare** (≥1/10,000 to <1/1000)
Immune system disorders	-	-	-	Hypersensitivity, angioneurotic oedema and anaphylactic reactions
Psychiatric Disorders	-	Insomnia*	-	-
Nervous system disorders	-	Headache*, dizziness*	-	-
Gastrointestinal disorders	Nausea	Hiccups, gastric symptoms e.g. flatulence, vomiting, stomatitis, oral discomfort., abdominal pain upper diarrhea, dry	-	-

		mouth, constipation.		
Cardiac disorders	-	-	Palpitations	Atrial arrhythmia (e.g. atrial fibrillation)
Respiratory, thoracic and mediastinal disorders	-	Pharyngitis, cough*, pharyngolaryngeal pain	-	-

*These events may also be due to withdrawal symptoms following smoking cessation.

Post Marketing Data

Table 2 shows events which were identified from post-marketing experience of nicotine oral forms. As these reactions are reported voluntarily from a population of uncertain size, the frequency of these reactions is unknown.

Table 2: Adverse Reactions from post-marketing data

System Organ Class	Adverse Reactions
Immune System Disorders	Hypersensitivity, angioedema, urticaria, ulcerative stomatitis, and very rare anaphylactic reactions.
Nervous System Disorders	Tremor.
Cardiac Disorders	Palpitations, tachycardia, arrhythmias, atrial fibrillation.
Respiratory, Thoracic and Mediastinal Disorders	Dyspnoea.
Gastrointestinal Disorders	Dysphagia, eructation, salivary hypersecretion.
General Disorders and Administration Site Conditions	Asthenia**, fatigue**, malaise**, influenza type illness**

**These events may also be due to withdrawal symptoms following smoking cessation.

Certain symptoms which have been reported such as dizziness, headache and insomnia may be ascribedto withdrawal symptoms in connection with smoking cessation and may be due to insufficient administration of nicotine.

Cold sores may develop in connection with smoking cessation, but any relation with the nicotine treatment is unclear.

The patient may still experience nicotine dependence after smoking cessation.

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 via HPRA Pharmacovigilance: Website: www.hpra.ie

4.9 Overdose

In overdose, symptoms corresponding to heavy smoking may be seen.
Even small quantities of nicotine are dangerous in children and may result in severe symptoms of poisoning which may prove fatal. If poisoning is suspected in a child, a doctor must be consulted immediately.

Overdose with Nicotinell Mint 2 mg Lozenge may only occur if many pieces are sucked simultaneously. Nicotine toxicity after ingestion will most likely be minimised as a result of early nausea and vomiting that occur following excessive nicotine exposure.

Signs and symptoms of an overdose from nicotine lozenge would be expected to be the same as those of acute nicotine poisoning, including: weakness, perspiration, pallor, hyperhidrosis, salivation, throat burn, nausea, vomiting, diarrhoea, abdominal pain, hearing and visual disturbances (sensory disturbance), headache, tachycardia and cardiac arrhythmia, dizziness, tremor, confusional state, and asthenia. Prostration, hypotension, circulatory collapse, coma, respiratory failure and terminal convulsions may ensue with large overdoses.

Treatment of overdose:

In the event of an overdose (e.g., too many lozenges ingested) medical attention should be sought immediately. All nicotine intake should cease immediately, and the patient be treated symptomatically, and vital signs monitored.

Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: N07B A01
Pharmacotherapeutic group: Drugs used in nicotine dependence

Mechanism of action
Nicotine, the primary alkaloid in tobacco products and a naturally occurring autonomous substance, is a nicotine receptor agonist in the peripheral and central nervous systems and has pronounced CNS and cardiovascular effects. On consumption of tobacco products, nicotine has proven to be addictive, resulting in craving and other withdrawal symptoms when administration is stopped. This craving and these withdrawal symptoms include a strong urge to smoke, dysphoria, insomnia, irritability, frustration or anger, anxiety, concentration difficulties, agitation and increased appetite or weight gain. The lozenge replaces part of the nicotine that would have been administrated via tobacco and reduces the intensity of the withdrawal symptoms and smoking urge.

5.2 Pharmacokinetic properties

Absorption
The absorbed amount of nicotine depends on the amount released into the mouth and absorbed through the buccal mucosa.

The main part of nicotine in Nicotinell Mint 2 mg Lozenge is absorbed through the buccal mucosa. A proportion, by the swallowing of nicotine containing saliva, reaches the stomach and intestine where it is inactivated. Due to the first-pass effect in the liver, the systemic bioavailability of nicotine is low.Consequently, in the treatment with Nicotinell Mint 2 mg Lozenge the high and quick systemic nicotine concentration, as seen when smoking, is rarely obtained.

The peak value for the plasma concentration of Nicotinell Mint 2 mg Lozenge after a single dose is approximately 7.0 ng per ml and the maximal concentration at steady state (one 2 mg lozenge/hour for 12 hours) is approximately 22.5 ng per ml (average plasma concentration of nicotine after smoking one cigarette is 15-30 ng per ml). Peak plasma concentration is reached after about 48 minutes following sucking of a single lozenge and after about 30 minutes at steady state.

Distribution
Distribution volume after intravenousadministration of nicotine is approximately 2-3 1/kg and the half-life is 2 hours. Nicotine ismetabolised principally in the liver and the plasma clearance is approximately 1.2 l/min; nicotine also metabolises in the kidney and lungs. Nicotine crosses the blood-brain barrier.

Metabolism
More than 20 metabolites have been identified, all believed to be less active than nicotine. The main metabolite is cotinine which has a half-life of 15-20 hours and with approximately 10 times higher plasma concentration than nicotine. Nicotine's plasma-protein binding is less than 5%. Changes in nicotine binding from the use of concomitant medicinal products or due to altered disease state are not expected to have significant effect on nicotine kinetics. The main metabolite in urine is cotinine (15% of the dose) and trans-3-hydroxy cotinine (45% of the dose).

Elimination
About 10% of the nicotine is excreted unchanged. Up to 30% may be excreted with urine in increased diuresis and the acidity under pH 5.

Studies have demonstrated that there is a linear dose-concentration proportionality between the 1 mg and 2 mg Nicotinell Lozenges for both C_{max} and AUC. The T_{max} are similar for both strengths.

5.3 Preclinical safety data

Nicotine was positive in some *in vitro* genotoxicity tests but there are also negative results with the same test systems. Nicotine was negative in standard *in-vivo* tests.
Animal experiments have shown that nicotine induces post-implantation loss and reduces the growth of foetuses.
The results of carcinogenicity assays did not provide any clear evidence of a tumorigenic effect of nicotine.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maltitol (E965)
Sodium carbonate anhydrous
Sodium hydrogen carbonate
Polyacrylate dispersion 30 per cent
Xanthan gum
Colloidal anhydrous silica
Levomenthol
Peppermint oil
Aspartame (E951)
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

12, 36, 72, 96, 144 or 204 lozenges in opaque blisters consisting of PET/aluminum foil and PVC/PE/PVDC/PE/PVC-film.
or
24, 72, 96 or 144 lozenges in polypropylene tube with an attached closure cap and an integrated desiccant sleeve of molecular sieve along the inner wall of the tube. Each tube contains 24 lozenges. Packs may contain 1, 3, 4 or 6 tubes.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Dr. Reddy's Netherlands B.V.
Claude Debussylaan 10
Amsterdam
Noord-Holland
1082 MD
Netherlands

8 MARKETING AUTHORISATION NUMBER

PA25456/001/005

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 04 November 2003

Date of last renewal: 16 December 2008

10 DATE OF REVISION OF THE TEXT

May 2026