SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Zonnic Pepparmint 1mg/spraying, oromucosal spray

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

0.07 ml contains 1 mg nicotine, which corresponds to 1 mg nicotine per spraying.
Excipient with known effect: ethanol

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oromucosal spray
A clear solution with a faint scent of peppermint.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of tobacco dependence by relieving nicotine craving and withdrawal symptoms, thereby facilitating smoking cessation in smokers motivated to quit or to facilitate smoking reduction in smokers who are not able or willing to quit smoking.

4.2 Posology and method of administration

Posology

Adults and elderly
The oromucosal spray should be sprayed 1-2 times between the cheek and the teeth when cigarettes normally would have been smoked or if cravings emerge. If after a single spray cravings are not controlled within a few minutes, a second spray should be used. If 2 sprays are required, future doses may be delivered as 2 consecutive sprays. Most smokers will require 1-2 sprays every 30 minutes to 1 hour.
. Up to 4 sprays per hour may be used. Do not exceed 2 sprays per dosing episode and do not exceed 64 sprays (4 sprays per hour, over 16 hours) in any 24-hour period.

Paediatric population
Zonnic Pepparmint should not be administered to adolescents (12-17 years of age) without recommendations from a health care professional.

Zonnic Pepparmint should not be administered to children below 12 years of age.

Smoking cessation
The duration of treatment is individual. Normally, the treatment should continue for at least 3 months. Gradual weaning from the oromucosal spray should then be initiated. Treatment should be discontinued when the dose is reduced to 1-2 sprayings per day. Regular use of Zonnic Pepparmint for more than 1 year is generally not recommended. In some cases a longer treatment period might be necessary in order to avoid relapse. Any spare oromucosal spray should be retained, as craving may suddenly occur.

Smoking reduction
Zonnic Pepparmint is used between periods of smoking in order to extend the smoke-free intervals and with regard to reduce smoking as much as possible. Professional help should be consulted if a decrease in number of cigarettes has not been achieved after 6 weeks of treatment.

An attempt to quit smoking should be made as soon as the smoker is motivated, however no later than 6 months after treatment start. Professional help should be consulted if there is no possibility to perform a serious attempt to quit smoking within 9 months. Regular use of Zonnic Pepparmint for more than 1 year is generally not recommended. Some ex- smokers may need treatment with the oromucosal spray for a longer period in order to avoid relapse. Any spare oromucosal spray should be retained, as craving may suddenly occur.

Method of administration
The oromucosal spray should be sprayed between the cheek and the teeth. The spray nozzle should be turned to the side and thereafter direct the oromucosal spray between the cheek and the teeth. Spray 1-2 times and alter between the left and right cheek.

Subjects should not eat or drink when administering the oromucosal spray.

Behavioural therapy advice and support will normally improve the success rate.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Those who have never used tobacco.
- Children under 12 years.

4.4 Special warnings and precautions for use

The benefits of quitting smoking outweigh any risks associated with correctly administered nicotine replacement therapy (NRT).

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, the oromucosal spray 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 NRT is initiated as reduction in nicotine induced catecholamine release can affect carbohydrate metabolism.

- *Allergic reactions*: Susceptibility to angioedema and urticaria.

- *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:* Use with caution in patients with uncontrolled hyperthyroidism or phaeochromocytoma as nicotine causes release of catecholamines.

• *Gastrointestinal Disease:* Nicotine may exacerbate symptoms in patients suffering from oesophagitis, gastric or peptic ulcers and NRT preparations should be used with caution in these conditions.

Paediatric population
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 can occur but is both less harmful 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 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.

Excipients: The oromucosal spray contains small amounts of ethanol (alcohol), less than 100 mg per spray.

Care should be taken not to spray the eyes whilst administering the oromucosal spray.

4.5 Interaction with other medicinal products and other forms of interaction

No clinically relevant interactions between nicotine replacement therapy and other drugs have definitely been established. However nicotine may possibly enhance the haemodynamic effects of adenosine i.e. increase in blood pressure and heart rate and also 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 is to be both non-smoking, and not using NRT.
Whilst smoking may have adverse effects on male fertility, no evidence exists that particular contraceptive measures are required during NRT 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 to the foetus and affects its breathing movements and circulation. The effect on the circulation is dose-dependent.

Therefore the pregnant smoker should always be advised to stop smoking completely without use of nicotine replacement therapy. The risk of continued smoking may pose greater hazard to the foetus as compared with the use of nicotine replacement products in a supervised smoking cessation programme. Use of Zonnic Pepparmint by the pregnant smoker should only be initiated after advice from a healthcare professional.

Breastfeeding
Nicotine passes freely into breast milk in quantities that may affect the child even with therapeutic doses. Zonnic Pepparmint should therefore be avoided during breast-feeding. Should smoking cessation not be achieved, use of Zonnic Pepparmint by breast feeding smokers should only be initiated after advice from a healthcare professional. Women should take the product just after having breastfed and leave as long a time as is possible (2 hours is suggested) between taking the mouth spray and the next feed.

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

Zonnic Pepparmint has no or negligible influence on the ability to drive and 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.

Zonnic Pepparmint may cause adverse reactions similar to those associated with nicotine given by other means and these are mainly dose-dependent. Allergic reactions such as angioedema, urticaria or anaphylaxis may occur in susceptible individuals.

Local adverse effects of administration are similar to those seen with other orally delivered forms. During the first few days of treatment irritation in the mouth and throat may be experienced, and hiccups are particularly common. Tolerance is normal with continued use.

Daily collection of data from trial subjects demonstrated that very commonly occurring adverse events were reported with onset in the first 2-3 weeks of use of the oromucosal spray, and declined thereafter.

Adverse reactions with oromucosal nicotine formulations identified from clinical trials and during post-marketing experience are presented below. The frequency category has 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 Reactions**
Immune system disorders	
Common	Hypersensitivity
Not known	Allergic reactions including angioedema and anaphylaxis
Psychiatric disorders	
Uncommon	Abnormal dream
Nervous system disorders	
Very common	Headache
Common	Dysgeusia, paraesthesia
Eye disorders	
Not known	Blurred vision, lacrimation increased
Cardiac disorders	

Uncommon	Palpitations, tachycardia, atrial fibrillation
Vascular disorders	
Uncommon	Flushing, hypertension
Respiratory, thoracic and mediastinal disorders	
Very common	Hiccups, throat irritation
Uncommon	Bronchospasm, rhinorrea, dysphonia, dyspnoea, nasal congestion, oropharyngeal pain, sneezing, throat tightness
Gastrointestinal disorders	
Very common	Nausea
Common	Abdominal pain, dry mouth, diarrhoea, dyspepsia, flatulence, salivary hypersecretion, stomatitis,, vomiting.
Uncommon	Eructation, gingival bleeding, glossitis, oral mucosal blistering and exfoliation, paraesthesia oral
Rare	Dysphagia, hypoaesthesia oral, retching
Not known	Dry throat, gastrointestinal discomfort, lip pain
Skin and subcutaneous tissue disorders	
Uncommon	Hyperhidrosis, pruritus, rash, urticaria
Not known	Erythema
General disorders and administration site conditions	
Common	Burning sensation, fatigue
Rare	Asthenia, chest discomfort and pain, malaise

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 the national reporting system listed in
[To be completed nationally]

4.9 Overdose

When used as directed, symptoms of overdose with nicotine may occur in patients with low pre-treatment nicotine intake or if other sources of nicotine are used concomitantly.

Symptoms of overdose are those of acute nicotine poisoning and include nausea, vomiting, increased salivation, 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.

Paediatric population
Doses of nicotine that are tolerated by adult smokers during treatment may produce severe symptoms of poisoning in small children and may prove fatal. 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: Drugs used in nicotine dependence

ATC code: N07BA01

Nicotine is an agonist at nicotine receptors in the peripheral and central nervous system and has pronounced CNS and cardiovascular effects.

Abrupt cessation of the use of tobacco-containing products results in the characteristic syndrome, with withdrawal symptoms including cravings (urges to smoke).

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

Compared with nicotine gum or nicotine lozenge, the absorption of nicotine from the oromucosal spray is more rapid (section 5.2).
In an open-label, single-dose crossover craving study in 48 healthy smokers it was observed that one and two sprays of 1 mg Zonnic oromucosal spray reduced the urge to smoke significantly more than nicotine lozenge 4 mg, at 1 minute after administration. It has not been shown that the properties of the spray formulation made any difference with respect to quitting smoking.

5.2 Pharmacokinetic properties

Absorption
The amount of released nicotine being absorbed from a nicotine oromucosal spray depends on the amount of nicotine released in the oral cavity and the amount thereof that is swallowed. The main part of nicotine released is absorbed through the buccal mucosa. The systemic bioavailability of swallowed nicotine is lower due to first- passage elimination.

In normal case approximately 1 mg of nicotine is released from one dose of oromucosal spray.

Nicotine uptake from the oral nicotine spray was detected at 4 min, the first timepoint tested. In the same study, nicotine was not detected at 4 min after nicotine lozenge administration. The median Tmax was 30 minutes (range 4 to 120 minutes) after administration of a 1 or 2 mg dose of the spray. The maximum plasma concentration was 3.1 and 5.2 ng/ml and AUC_{inf} was 10 and 17 h*ng/ml after a 1 and 2 mg dose, respectively.

Distribution
The volume of distribution following i.v. administration of nicotine is about (2-) 3 l/kg and its half-life is about 2 hours. Other diseases or concomitant use of other drugs which influence levels of plasma proteins are not expected to have any significant effect on the kinetics of nicotine.

Biotransformation
Nicotine is metabolized mainly in the liver and plasma clearance is in average about 70 l/ hour. Nicotine is metabolized also in kidneys and lungs. More than 20 metabolites are identified whereof all are believed to be less active than nicotine. The primary metabolite of nicotine is cotinine which has a half-life 15-20 hours and which give plasma concentrations that exceed nicotine by 10-fold. Plasma protein binding is less than 5 %.

Elimination
The major metabolites in urine are cotinine (15 % of the dose) and trans-3-hydroxycotinin (45% of the dose). About 10% of nicotine is excreted unchanged in the urine. As much as 30% of nicotine may be excreted in the urine at increased diuresia and acidification of the urine below pH 5.

Special populations
Heavily impaired kidney function is assumed to exert influence on total clearance of nicotine.

The pharmacokinetics of nicotine is unaffected in cirrhotic patients with mild liver impairment (Child score 5) and decreased in liver cirrhosis patients with moderately liver impairment (Child score 7). Increased nicotine levels have been observed in smoking haemodialysis patients.

Minor reduction of total clearance of nicotine has been demonstrated in healthy, elderly users, however, adjusting of the dose is not necessary.

No differences in nicotine kinetics have been observed between males and females.

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 *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

Sucralose
Mint flavour
Ethanol
Glycerol
Potassium dihydrogen phosphate
Sodium hydroxide
Water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container

Vial of glass or plastic (PET) with accuator made of polypropylene. Each vial contains 3 ml (40 sprayings) or 15 ml (200 sprayings).
Package sizes:
40 sprayings
200 sprayings
400 (2 x 200) sprayings

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Niconovum AB
Box 31008
SE-200 49 Malmö
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

25810

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 2008-06-26
Date of latest renewal: 2013-06-26

10. DATE OF REVISION OF THE TEXT

2024-03-08