Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Nicorette Quickmist 1 mg/spray oromucosal spray, solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One spray delivers 1 mg nicotine in 0.07 ml solution. 1 ml solution contains 13.6 mg nicotine.

Excipient with known effect:
Ethanol 7.1 mg/spray
Propylene glycol 11 mg/spray
Butylated hydroxytoluene 363 ng/spray

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oromucosal spray, solution

A clear to weakly opalescent, colourless to light yellow solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Nicorette QuickMist is to be used for the treatment of tobacco dependence in adults by relief of nicotine withdrawal symptoms, including cravings, during a quit attempt or to cut down smoking before stopping completely. Permanent cessation of tobacco use is the final objective. Nicorette QuickMist should preferably be used in conjunction with a behavioral support program.

4.2 Posology and method of administration

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

Adults and Elderly
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.

Abrupt Smoking Cessation
For Smokers willing and ready to stop smoking immediately.

Subjects should stop smoking completely during the course of treatment with Nicorette QuickMist.

The following chart lists the recommended usage schedule for the oromucosal spray during full treatment (Step I) and during tapering (Step II and Step III).

Step I: Weeks 1-6
Use 1 or 2 sprays 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.

Step II: Weeks 7-9
Start reducing the number of sprays per day. By the end of week 9 subjects should be using HALF the average number of sprays per day that was used in Step I.

Step III: Weeks 10-12
Continue reducing the number of sprays per day so that subjects are not using more than 4 sprays per day during week 12. When subjects have reduced to 2-4 sprays per day, oromucosal spray use should be discontinued.

Example: If an average of 15 cigarettes per day are usually smoked, 1-2 sprays should be used at least 15 times during the day.

To help stay smoke free after Step III, subjects may continue to use the oromucosal spray in situations when they are strongly tempted to smoke. One spray may be used in situations where there is an urge to smoke, with a second spray if one spray does not help within a few minutes. No more than four sprays per day should be used during this period.

Gradual cessation through progressive reduction in smoking
For smokers who are not willing or ready to quit abruptly.

The oromucosal spray is used between periods of smoking in order to prolong the smoke-free intervals and with the intention to reduce smoking as much as possible. The patient should be aware that an incorrect use of the spray may enhance adverse effects.

A cigarette is replaced with one dose (1-2 sprays) and a quit attempt should be made as soon as the smoker feels ready and no later than 12 weeks after start of treatment. If a reduction in cigarette consumption has not been achieved after 6 weeks of treatment, a healthcare professional should be consulted. After quitting smoking, gradually reduce the number of sprays per day. When subjects have reduced to 2-4 sprays per day, oromucosal spray should be discontinued.

Regular use of the oromucosal spray beyond 6 months is not recommended. Some ex-smokers may need treatment with the oromucosal spray longer to avoid returning to smoking. Any remaining oromucosal spray should be retained to be used in the event of sudden cravings.

Paediatric population
Do not administer Nicorette QuickMist to persons under 18 years of age. There is no experience of treating adolescents under the age of 18 with Nicorette QuickMist.

Method of administration
After priming, point the spray nozzle as close to the open mouth as possible. Press firmly the top of the dispenser and release one spray into the mouth, avoiding the lips. Subjects should not inhale while spraying to avoid getting spray into the respiratory tract. For best results, do not swallow for a few seconds after spraying.

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

4.3 Contraindications

- Hypersensitivity to nicotine or to any of the excipients listed in section 6.1.
- Children under the age of 18 years.
- Those who have never smoked.

4.4 Special warnings and precautions for use

Nicorette QuickMist should not be used by non-smokers.

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: This medicine contains about 7 mg of alcohol (ethanol) in each spray which is equivalent to 97 mg/ml. The amount in one spray of this medicine is equivalent to less than 2 ml beer or 1 ml wine. The small amount of alcohol in this medicine will not have any noticeable effects.
This medicinal product contains less than 1 mmol sodium (23 mg) per spray, i.e. essentially 'sodium- free'. This medicine contains 11 mg propylene glycol in each spray which is equivalent to 150 mg/mL. Due to the presence of butylated hydroxytoluene, Nicorette QuickMist may cause local skin reactions (e.g. contact dermatitis), or irritation to the eyes and mucous membranes.

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 Nicorette QuickMist by the pregnant smoker should only be initiated after advice from a healthcare professional.

Lactation
Nicotine passes freely into breast milk in quantities that may affect the child even with therapeutic doses. Nicorette QuickMist should therefore be avoided during breast-feeding. Should smoking cessation not be achieved, use of Nicorette QuickMist 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

Nicorette Quickmist 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.

Nicorette QuickMist 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 to <1/10); uncommon (≥1/1 000 to <1/100); rare (≥1/10 000 to <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,
Not known	Atrial fibrillation
Vascular disorders	

Uncommon	Flushing, hypertension
Respiratory, thoracic and mediastinal disorders	
Very common	Hiccups, throat irritation
Common	Cough
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
Uncommon	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 HPRA Pharmacovigilance, Website: www.hpra.ie

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 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: Drug used in nicotine dependence.
ATC code: N07B A01

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 established, regular 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 raising blood nicotine levels and relieving these withdrawal symptoms.

Craving Relief
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 200 healthy smokers it was observed that two sprays of 1 mg reduced the urges to smoke significantly more than nicotine lozenge 4 mg, starting at 60 seconds after administration, and a difference between the formulations was observed for 10 minutes.
In another open-label, single-dose, crossover craving study in 61 healthy smokers it was observed that 2 sprays of 1 mg reduced the urge to smoke significantly more than the reference product, starting 30 seconds after administration in the study population, including the subset of subjects rating their baseline urges to smoke as severe. In addition, 53/58 (91%) and 45/58 (78%) of subjects reached 25% and 50% reduction in urges to smoke over the study period (i.e. 2h), respectively.

Smoking cessation
Two placebo-controlled efficacy studies have been performed. In the first study, 83/318 (26.1%) of participants using oromucosal spray managed to quit smoking at week 6 compared to 26/161 (16.1%) in the placebo group. At weeks 24 and 52 50/318 (15.7%) and 44/318 (13.8%), respectively in the oromucosal spray group and 11/161 (6.8%) and 9/161 (5.6%), respectively in the placebo group managed to quit smoking. In the second study, 30/597 (5.0%) of participants in the oromucosal spray group were smoke free at week 6 compared to 15/601 (2.5%) in the placebo group.

5.2 Pharmacokinetic properties

Variations in delivery format have been found to have significant effects on rate and extent of absorption.
The pharmacokinetics of the oromucosal spray has been studied in 4 studies. The studies included 141 subjects.

Absorption
A maximum concentration of 5.3 ng/mL is reached within 13 minutes after administration of a 2 mg dose. Comparing the AUC over the first 10 minutes after administration the estimates of the oromucosal spray at a dose of 1 and 2 mg exceeds those of nicotine gum as well as nicotine lozenge at doses of 4 mg (0.48 and 0.64 h*ng/mL vs. 0.33 and 0.33 h*ng/mL).

AUC_{∞} estimates show the bioavailability of nicotine administered by oromucosal spray is similar to that of nicotine gum or lozenge. The AUC_{∞} of the oromucosal spray 2 mg measured 14.0 h*ng/mL in comparison with 23.0 h*ng/mL and 26.7 h*ng/mL for nicotine gum 4 mg and nicotine lozenge 4 mg, respectively.

Steady-state average nicotine plasma concentrations achieved after administration of the maximum dose (i.e. 2 sprays of the oromucosal spray 1 mg every 30 minutes) are in the order of magnitude approximately 28.8 ng/mL as compared with 23.3 ng/mL for nicotine gum 4 mg (1 gum, hourly) and 25.5 ng/mL for nicotine lozenge 4 mg (1 lozenge, hourly).

Distribution
The volume of distribution following intravenous administration of nicotine is about 2 to 3 l/kg.

Plasma protein binding of nicotine is less than 5%. Therefore, changes in nicotine binding from use of concomitant drugs or alterations of plasma proteins by disease states would not be expected to have any significant effects on the nicotine pharmacokinetics.

Biotransformation
The major nicotine-eliminating organ is the liver, although the kidney and lung also metabolise nicotine. More than 20 metabolites of nicotine have been identified, all of which are believed to be less active than the parent compound.

The primary metabolite of nicotine in plasma, cotinine, has a half-life of 15 to 20 hours and concentrations that exceed nicotine by 10-fold.

Elimination
The average plasma clearance of nicotine is 70 l/hour and the half-life is 2-3 hours.

The primary urinary metabolites are cotinine (12% of the dose) and trans-3-hydroxy-cotinine (37% of the dose). About 10% of nicotine is excreted unchanged in the urine. As much as 30% of nicotine may be excreted unchanged in the urine with high flow rates and acidification of the urine below pH 5.

Linearity/non-linearity
There is only a small deviation from dose-linearity of AUC_{∞} and C_{max} as shown when single doses of 1, 2, 3 and 4 sprays of the 1 mg oromucosal spray are given.

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

Hepatic Impairment
The pharmacokinetics of nicotine are unaffected in patientswith mild liver impairment (Child-Pugh score 5) and decreased by 40-50% in patients with moderate liver impairment (Child-Pugh score 7). There is no information available in subjects with a Child-Pugh score > 7.

Elderly
A minor reduction in total clearance of nicotine, not justifying adjustment of dosage, has been demonstrated in healthy elderly patients.

5.3 Preclinical safety data

In vitro genotoxicity testing of nicotine has yielded predominantly negative results. There are some equivocal results when testing at high nicotine concentrations.

In vivo tests of genotoxicity have been negative.

Animal experiments have shown that nicotine exposure results in decreased birth-weight, decreased litter size and decreased survival of offspring.

Results of carcinogenicity assays do not provide any clear evidence of a tumorigenic effect of nicotine.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Propylene glycol (E1520)
Anhydrous ethanol
Trometamol
Poloxamer 407
Glycerol (E422)
Sodium hydrogen carbonate
Levomenthol
Mint flavour
Cooling flavour
Sucralose
Acesulfame potassium
Butylated hydroxytoluene (E321)
Hydrochloric acid (for pH adjustment)
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2.5 years.

6.4 Special precautions for storage

Do not store above 30°C

6.5 Nature and contents of container

13.2 ml solution is filled in a PET bottle. One bottle contains 150 sprays of 1 mg. The bottle is placed in a dispenser with a mechanical spray pump with an actuator. The dispenser has a child resistant feature.

Pack sizes
1x1 dispenser, 2x1 dispensers
1x1 dispenser + Near Field Communication (NFC), 2x1 dispensers + NFC: Includes an NFC chip underneath the back label of the dispenser to allow connectivity with a smartphone app.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Johnson & Johnson (Ireland) Limited
Airton Road
Tallaght
Dublin 24
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8 MARKETING AUTHORISATION NUMBER

PA0330/037/013

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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