SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Nicotine 1 mg/spray Mouth Spray

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

0.07 ml contains 1 mg nicotine, corresponding to 1mg nicotine per spray.

Excipients with known effect *(per spray)*: ethanol 18.4mg .

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

Nicotine Mouth Spray relieves and/or prevents craving and nicotine withdrawal symptoms associated with tobacco dependence. It is indicated to aid smokers wishing to quit or reduce prior to quitting, to assist smokers who are unwilling or unable to smoke, and as a safer alternative to smoking for smokers and those around them.

Nicotine Mouth Spray is indicated in pregnant and lactating women making a quit attempt.

Nicotine Mouth Spray should preferably be used in conjunction with a behavioural support programme.

4.2 Posology and method of administration

Posology

Adults and children over 12 years of age

Nicotine Mouth Spray should be sprayed between the cheek and the teeth. The spray nozzle should be turned to the side and thereafter the mouth spray directed between the cheek and the teeth. Alternate between the left and right cheek.

Use 1 or 2 sprays when cigarettes normally would have been smoked or if cravings emerge. If after the first 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.
You may use up to 4 sprays per hour. Do not exceed 2 sprays per dosing episode and 64 sprays (4 sprays per hour over 16 hours) in any 24-hour period.

Nicotine Mouth Spray should be used whenever the urge to smoke is felt or to prevent cravings in situations where these are likely to occur.

Smoking cessation
Smokers willing or able to stop smoking immediately should initially replace all their cigarettes with the Nicotine Mouth Spray and as soon as they are able, reduce the number of sprays used until they have stopped completely.

Smoking reduction
Smokers aiming to reduce cigarettes should use the mouth spray, as needed, between smoking episodes to prolong smoke-free intervals and with the intention to reduce smoking as much as possible.
As soon as they are ready smokers should aim to quit smoking completely.

When making a quit attempt behavioural therapy, advice and support will normally improve the success rate. Those who have quit smoking but are having difficulty discontinuing their mouth spray are recommended to contact their pharmacist or doctor for advice.

Method of administration
The patient should not eat or drink while using the mouth spray.
Care should be taken not to spray the eyes whilst administering the mouth spray.
Do not inhale while spraying to avoid getting spray down your throat.
For the best results, do not swallow for a few seconds after spraying.

When the spray is used for the first time, the spray pump must be primed. The spray nozzle should be pointed safely away from the user, any adults, children or pets nearby. The pump should be sprayed 5 times in the air until a fine spray appears. If the spray is not used for 7 days, this priming procedure will need to be repeated.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Nicotine Mouth Spray is contraindicated in children under 12 years and in non-smokers.

4.4 Special warnings and precautions for use

The risks associated with the use of Nicotine Replacement Therapy (Nicotine replacement Therapy) are substantially outweighed in virtually all circumstances by the well-established dangers of continued smoking.

Patients hospitalised for MI, severe dysrhythmia or CVA who are considered to be haemodynamically unstable should be encouraged to stop smoking with nonpharmacological interventions. If this fails, Nicotine Mouth Spray may be considered, but as data on safety in this patient group are limited, initiation should only be under medical supervision. Once patients are discharged from hospital they can use NRT as normal. If there is a clinically significant increase in cardiovascular or other effects attributable to nicotine, the dose should be reduced or discontinued.

Diabetes: Blood glucose levels may be more variable when stopping smoking, with or without NRT as catecholamines released by nicotine can affect carbohydrate metabolism, so it is important for diabetics to closely monitor their blood glucose levels while using this product.

Allergic reactions: Susceptibility to angioedema and urticaria.

A risk-benefit assessment should be made by an appropriate healthcare professional for patients with the following conditions:
• *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.
• *GI disease*: Swallowing of nicotine may exacerbate symptoms in persons suffering from active oesophagitis, oral or pharyngeal inflammation, gastritis, gastric ulcer or peptic ulcer and oral NRT preparations should be used with caution in these conditions. Ulcerative stomatitis has been reported.

• *Seizures:* Potential risks and benefits of nicotine should be carefully evaluated before use in subjects taking anticonvulsant therapy or with a history of epilepsy as cases of convulsions have been reported in association with nicotine.

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.

Stopping smoking: Polycyclic aromatic hydrocarbons in tobacco smoke induce the metabolism of drugs catalysed by CYP 1A2 (and possibly by CYP 1A1). When a smoker stops this may result in a slower metabolism and a consequent rise in blood levels of such drugs.

Transferred dependence: Transferred dependence is rare and is both less harmful and easier to break than smoking dependence.

Ethanol content: This medicinal product contains a small amount of ethanol (alcohol), less than 100mg per 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 increase pain response (angina-pectoris type chest pain) provoked by adenosine administration.

4.6 Fertility, Pregnancy and lactation

Pregnancy

Stopping smoking is the single most effective intervention for improving the health of both the pregnant smoker and her baby, and the earlier abstinence is achieved the better. However, if the mother cannot (or is considered unlikely to) quit without pharmacological support, NRT may be used as the risk to the fetus is lower than that expected with smoking tobacco. Stopping completely is by far the best option but NRT may be used in pregnancy as a safer alternative to smoking. Because of the potential for nicotine-free periods, intermittent dose forms are preferable, but patches may be necessary if there is significant nausea and/or vomiting. If patches are used they should, if possible, be removed at night when the fetus would not normally be exposed to nicotine.

Lactation

The relatively small amounts of nicotine found in breast milk during NRT use are less hazardous to the infant than second-hand smoke. Intermittent dose forms would minimize the amount of nicotine in breast milk and permit feeding when levels were at their lowest.

Fertility

In contrast to the well known adverse effects of tobacco smoking on human conception and pregnancy, with increased risk for infertility in both women and men, the effects of therapeutic nicotine treatment are unknown. Thus the most prudent state for women intending to become pregnant is to be both non-smoking, and not using NRT.

4.7 Effects on ability to drive and use machines

Nicotine Mouth Spray has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Nicotine Mouth Spray may cause adverse reactions similar to those associated with nicotine administered by other means, including smoking, and are dose dependent. Most of the undesirable effects reported by the patient usually occur during the first 2-3 weeks after treatment start, and are similar to those seen with other orally delivered forms. These can include 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.

Increased frequency of aphthous ulcer, cough and nasophyringitis may occur after abstinence from smoking. The causality is unclear.

During the first few days of treatment irritation to the mouth and throat may be experienced and hiccups are particularly common. Tolerance is normal with continued use.

In addition to this, other cessation associated symptoms were seen in those using a mouth spray: dizziness,
presyncopal symptoms, constipation, and gingival bleeding.

Nicotine craving, which is recognised as a clinically relevant symptom, is an important element in nicotine withdrawal after smoking cessation.

Reported adverse events associated with nicotine mouth sprays include:

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).

BODY SYSTEM	UNDESIRABLE EFFECTS
Nervous system disorders:	
Very common	Dysgeusia, headache
Common	Dizziness
Uncommon	Paraesthesia
Eye disorders:	
Uncommon	Lacrimation increase
Not known	Vision blurred
Cardiac disorders:	
Uncommon	Palpitations
Not known	Atrial fibrillation
Vascular disorders:	
Uncommon	Flushing
Respiratory, thoracic and mediastinal disorders:	
Very common	Hiccups
Uncommon	Rhinorrhoea, dyspnoea, bronchospasm, sneezing, nasal congestion
Skin and subcutaneous tissue disorders:	
Uncommon	Dry skin, hyperhydrosis, rash, urticaria, pruritus
Gastrointestinal disorders:	
Very common	Nausea and dyspepsia
Common	Vomiting, flatulence, abdominal pain, diarrhoea
Uncommon	Gingivitis, glossitis
Immune system disorders:	
Uncommon	Hypersensitivity
Musculoskeletal, connective tissue and bone disorders:	
Uncommon	Musculoskeletal pain
General disorders and administration site conditions:	
Very common	Oral soft tissue pain and paraesthesia, stomatitis, salivary hypersecretion, burning lips, dry mouth and/or throat
Common	Throat tightness, fatigue, chest pain and discomfort and toothache
Uncommon	Oral mucosal exfoliation, dysphonia

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 MHRA Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

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 pallor, nausea, salivation, vomiting, abdominal pain, diarrhoea, sweating, headache, dizziness, disturbed hearing and vision, tremor, mental confusion and marked weakness. At high doses, these symptoms may be followed by hypotension, rapid or weak and irregular pulse, breathing difficulties, prostration, circulatory collapse and convulsions (including terminal convulsions).

The minimum lethal dose of nicotine in a non tolerant man has been estimated to be 40 to 60 mg. Even small quantities of nicotine may be dangerous in children and may prove fatal. Suspected nicotine poisoning in a child should be considered a medical emergency and treated immediately.

Management of overdose:

In the event of an overdose (e.g. too many sprays used) the user should seek medical attention immediately. All intake of nicotine must be stopped immediately and the patient should be treated symptomatically. Artificial respiration with oxygen should be instituted if necessary. Activated charcoal reduces the gastrointestinal absorption of nicotine.

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. When consumed in tobacco products, it has been shown to be addictive and abstinence is linked to craving and withdrawal symptoms.

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 smoking by relieving these withdrawal symptoms.

In an open-label, single-dose crossover craving study in 48 healthy smokers it was observed that one and two sprays of 1 mg Nicotine Mouth Spray reduced the urge to smoke significantly more than nicotine lozenge 4 mg, at 1 minute after administration. However, there was no or little difference at the 5 minute time point. 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 mouth 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.

Approximately 1 mg of nicotine is released from one spray dose of mouth spray.

In an open-label, single-dose pharmacokinetic study in 20 healthy smokers, nicotine uptake from the oral nicotine spray was detected at 4 min, the first time point tested. The median Tmax was 27 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

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: In smokers with liver cirrhosis but only mild liver impairment (Child-Pugh score 5) the pharmacokinetics of nicotine is unaffected. However, in smokers with moderately impaired liver (Child-Pugh score 7) total clearance has been reported to be reduced by 40-50%. There is no information available in subjects with a Child-Pugh score > 7.

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

5.3 Preclinical safety data

The general toxicity of nicotine is well known and taken into account in the recommended posology. Nicotine was not mutagenic in appropriate assays. The results of carcinogenicity assays did not provide any clear evidence of a tumorigenic effect of nicotine. In studies in pregnant animals, nicotine showed maternal toxicity, and consequential mild foetal toxicity. Additional effects included pre and postnatal growth retardation and delays and changes in postnatal CNS development. Effects were only noted following exposure to nicotine at levels in excess of those which will result from recommended use of Nicotine Mouth Spray. Effects on fertility have not been established. Comparison of the systemic exposure necessary to elicit these adverse responses from preclinical test systems with that associated with the recommended use of Nicotine Mouth Spray indicate that the potential risk is low and outweighed by the demonstrable benefit of nicotine therapy in smoking cessation. However, the Nicotine Mouth Spray should only be used by pregnant women on medical advice if other forms of treatment have failed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucralose

Peppermint 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.

6.5 Nature and contents of container

Plastic (PET) bottle with actuator made of polypropylene. Each vial contains 6.8 ml (40 sprays) or 17.2 ml (200 sprays). A pack of 2 x 200 sprays is also available. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 48339/0001

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