SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Nicorette Microtab 2 mg sublingual tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One tablet contains 17.1 mg of nicotine betadex equivalent to 2 mg nicotine.

Excipients with known effects:
Betadex (β-cyclodextrin) (84.5mg/tablet)

For the full list of excipients see section 6.1

3. PHARMACEUTICAL FORM

Sublingual tablet

White to off-white, circular flat bevel-edged tablets engraved 'NIC' on one side and '2' on the opposite side.

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.

Advice and support normally improve the success rate.

4.2 Posology and method of administration

Paediatric Population
In adolescents (age 12 to 17 years), Nicorette Microtab should only be used with advice from a Healthcare Professional.

Nicorette Microtab is not recommended for use in children under 12 years of age due to lack of data on safety and efficacy.

The patient should stop smoking completely during treatment with Nicorette Microtab.

Adults and Elderly
Nicorette Microtab should be placed under the tongue where it dissolves slowly (about 30 minutes). It should not be swallowed or chewed.

The initial dosage should be individualised on the basis of the patient's nicotine dependence. Low dependent smokers (Fagerström Test criteria or smoking ≤20 cigarettes/day) should use the 2 mg tablet. Highly dependent smokers (FagerströmTest criteria or smoking > 20 cigarettes/day) or patients who have failed to stop smoking with the 2 mg tablet should use

the 4 mg strength. Initially, one tablet should be taken every 1 to 2 hours; 8-12 tablets per day will usually be adequate. Two tablets of the 2 mg strength could be used as an alternative to one 4 mg tablet. No more than thirty 2 mg sublingual tablets should be used per day.

The duration of treatment is individual, but is normally at least 2 to 3 months. Gradual weaning from the tablets should then be initiated. Treatment should be stopped when the dose is reduced to 1-2 tablets per day. Any spare tablets should be retained, as craving may suddenly occur.

Regular use of Nicorette Microtab beyond 6 months is generally not recommended. Some exsmokers may need treatment with the tablet longer to avoid returning to smoking.

4.3 Contraindications

- Hypersensitivity to nicotine or to any of the excipients listed in section 6.1.
- Children under the age of 12 years
- Those who have never smoked

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, Nicorette Microtab 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 reductions 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.

- *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).

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 unusual and 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. 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 drugs 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.
Nicorette Microtab contains 84.5 mg betadex (β-cyclodextrin) in each tablet.

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 for more information on altered metabolism of certain drugs when 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 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 effecton the circulation is dose-dependent.

Therefore the pregnant smoker should always be advised to stop smoking completely withoutuse of nicotine replacement therapy. The risk of continued smoking may pose greater

hazardto the foetus as compared with the use of nicotine replacement products in a supervisedsmoking cessation programme. Use of the sublingual tablet by the pregnant smoker should only be initiated after advice from a health professional.

Lactation
Nicotine passes freely into breast milk in quantities that may affect the child even withtherapeutic doses. Nicorette Microtab should therefore be avoided during breast-feeding. Should smoking cessation not be achieved, use of the sublingual tablets by breast feeding smokers should only be initiated after advice from a health professional. Where nicotine replacement therapy is used whilst breast-feeding, the sublingual tablets should be taken just after breast feeding and not during the two hours before breast feeding.

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

4.7 Effects on ability to drive and use machines

Nicorette Microtab 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 Microtab may cause adverse reactions similar to those associated with nicotine administered by other means and are dose-dependent.

Most of the undesirable effects reported by the patient occur during the first 3-4 weeks after start of treatment. During the first few days of treatment irritation in mouth and throat may be experienced. Nearly all patients will get used to this sensation after these first days.

Allergic reactions (including symptoms of anaphylaxis) occur rarely during use of Nicorette Microtab.

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) .

Immune system disorders	
Common	Hypersensitivity
Not known	Anaphylactic reaction
Psychiatric disorders	
Uncommon	Abnormal dream
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 fibrilation
Vascular disorders	
Uncommon	Flushing, hypertension
Respiratory, thoracic and mediastinal disorders	
Very common	Cough, 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	Angioedema, erythema
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.

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 Appendix V.

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 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.

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
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.

5.2 Pharmacokinetic properties

The amount of nicotine absorbed from Nicorette Microtab depends on the amount of nicotine released in the oral cavity and the amount thereof that is swallowed. The main part of nicotine released from a tablet is absorbed through the buccal mucosa. The absolute bioavailability of nicotine after sublingual administration of the tablet is approx. 50%. The systemic bioavailability of swallowed nicotine is lower due to first pass elimination. The high and rapidly rising nicotine concentrations seen after smoking are rarely produced by treatment with Nicorette Microtab.

Steady-state trough nicotine plasma concentrations achieved after 10 hourly doses of 1 tablet are in the order of magnitude of 10 ng/ml. After *ad libitum* use the nicotine plasma concentration is about 8 ng/ml, which is approximately half of the nicotine level obtained in low to medium dependent smokers.

There is a slight deviation from dose-linearity of AUC_{inf} and C_{max} when single doses of 1, 2 and 3 tablets are given. This deviation may be explained by a larger fraction of the higher doses being swallowed and subject to first pass elimination.

The volume of distribution following i.v. 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 significant effects on nicotine kinetics.
The major eliminating organ is the liver, and average plasma clearance is about 70 L/hour and the half-life is approximately 2 hours. 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.

The primary urinary metabolites are cotinine (15% of the dose) and trans-3-hydroxy-cotinine (45% 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.

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

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

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

Betadex (β-cyclodextrin)
Crospovidone
Magnesium stearate
Colloidal anhydrous silica

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Package sizes:
Cardboard box of 30 or 105 sublingual tablets with a dispenser. The tablets are packed in blister packages of 15 tablets/blister. The blister consists of a PVC/PVDC film and a foil, composed of polyester, aluminium and paper. The dispenser is made of polypropylene.

Cardboard box of 20, 30, 90, 100 or 150 sublingual tablets. A carry case may be included. The tablets are packed in aluminium/aluminium blisters of 10 tablets per blistercard.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

<To be completed nationally>

8. MARKETING AUTHORISATION NUMBER(S)

<To be completed nationally>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

1997-02-14/2007-01-01

10. DATE OF REVISION OF THE TEXT

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2023-06-28