IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0823/049/019
Case No: 2043019

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

McNeil Healthcare (Ireland) Ltd

Airton Road, **Tallaght**, **Dublin 24**, **Ireland**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Nicorette Microtab Lemon Sublingual Tablets 2mg

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **08/04/2008** until **05/07/2012**.

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Nicorette Microtab Lemon Sublingual Tablets 2mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Nicotine bitartrate corresponding to nicotine 2.0 mg nicotine per tablet.

Also contains Aspartame
For a full list of excipients see section 6.1

3 PHARMACEUTICAL FORM

Sublingual tablet.
White to off-white flat round, bevel-edged tablets engraved on one side with ‘N2’.

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, helping smokers to temporarily abstain from smoking.

4.2 Posology and method of administration

Children and Adolescents
Nicotine sublingual tablet should not be administered to persons under 18 years of age without recommendation from a health care professional. There is no experience of treating this age group with nicotine sublingual tablets.

Adults and the Elderly
Smoking Cessation

The initial dose is based on the individual’s nicotine dependence. Low dependent smokers should use the 2-mg tablet. Highly dependent smokers (Fagerström Test for Nicotine Dependence (FTND) ≥ 6 or smoking > 20 cigarettes/day) or patients who have failed to stop smoking with the 2-mg sublingual tablet should use the 4-mg strength. Initially, one tablet should be taken every 1 to 2 hours; 8-12 tablets of the appropriate strength 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 forty 2-mg sublingual tablets or twenty 4-mg sublingual tablets should be used per day. If not successful after 12 weeks the patient should be encouraged to make a fresh attempt to stop smoking. This may necessitate full or partial re-treatment with an NRT programme.

Advise and support normally improve the success rate.

Adults and the Elderly – Temporary Abstinence

During periods of temporary abstinence, the patient should use one tablet per hour, or for heavy smokers, two tablets

per hour, to relieve nicotine cravings and withdrawal symptoms.
Increasing to two tablets per hour may be considered for patients who find the one tablet per hour regimen is not relieving their cravings.

Children

The safety of Nicorette Microtab has not been established in individuals under eighteen years of age. The product should only be used in these subjects under medical supervision.

Concomitant Disease
Only severe renal impairment would be expected to affect the clearance of nicotine or its metabolites from the circulation. In patients smoking and undergoing renal haemodialysis, elevated nicotine levels have been seen.

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

4.3 Contraindications

Hypersensitivity to any component of the sublingual tablet.

4.4 Special warnings and precautions for use

Nicotine sublingual tablet should only be used after consulting a physician by particular cardiovascular patient groups: those who have experienced a serious cardiovascular event, or hospitalisation for a cardiovascular complaint, in the previous 4 weeks (e.g. stroke, myocardial infarction, unstable angina, cardiac arrhythmia, coronary artery bypass graft and angioplasty) or where they suffer with uncontrolled hypertension.

Nicotine sublingual tablet should be used with caution in patients with severe/moderate hepatic impairment, severe renal impairment, active duodenal and gastric ulcers.
Nicotine, both from NRT and smoking, causes the release of catecholamines from the adrenal medulla. Therefore nicotine sublingual tablet should also be used with caution in patients with uncontrolled hyperthyroidism or pheochromocytoma.

Patients with diabetes mellitus may require lower doses of insulin as a result of smoking cessation.

Some users may continue to use nicotine sublingual tablet after the recommended treatment period, but the potential risk of longer-term use is far less than those associated with resuming to smoking.

4.5 Interaction with other medicinal products and other forms of interaction

Smoking (but not nicotine) is associated with increase in CYP1A2 activity. After cessation of smoking, reduced clearance of substrates for this enzyme may occur. This may lead to an increase in plasma levels for some medicinal products 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.

4.6 Pregnancy and lactation

Pregnancy
Nicotine passes to the foetus and affects its breathing movements and circulation. The effect on the circulation is dose-dependent.

Smoking can seriously harm the foetus and should be stopped. Pregnant smokers should only use nicotine sublingual tablet after consulting a health care professional. The risks for the foetus from nicotine sublingual tablet are not fully known. The benefits of nicotine replacement therapy in pregnant women who cannot abstain without such therapy substantially outweigh the risk of continued smoking.

Lactation
Nicotine passes into breast milk in small quantities that may affect the infant, even at therapeutic doses. To reduce the exposition to the child the nicotine sublingual tablet should be used just after breast-feeding.

4.7 Effects on ability to drive and use machines

Nicotine sublingual tablet has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Nicotine sublingual tablet 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 patients occur during the first 3-4 weeks after start of treatment.

Some symptoms, such as dizziness, headache and sleeplessness may be related to withdrawal symptoms associated with abstinence from smoking. Increased frequency of aphtous ulcer may occur after abstinence from smoking. The causality is unclear.

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), including isolated reports.

Nervous system disorders: Common: Dizziness, headache

Cardiac disorders: Common: Palpitations
Very rare: Reversible atrial fibrillation

Repiratory, thoracic and mediastinal disorders: Common: Coughing,

Gastrointestinal disorders: Common: Gastrointestinal discomfort, hiccups, nausea

General disorders and administration site conditions: Common: Sore mouth or throat, dry mouth, burning sensation in the mouth, rhinitis.

4.9 Overdose

Excessive use of nicotine from either NRT and/or smoking might cause symptoms of an overdose.

Symptoms of overdosage are those of acute nicotine poisoning and include nausea, 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 small children and may prove fatal.

Management of overdosage: Administration of nicotine must be stopped immediately and the patient should be treated symptomatically. Activated charcoal reduces the gastrointestinal absorption of nicotine.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drug for treatment of addiction.
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 nicotine sublingual tablet 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 the nicotine sublingual tablet.

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 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

There are no pre-clinical data on the safety of nicotine sublingual tablets.

The toxicity of nicotine as a component of tobacco is, however, well documented. Typical symptoms of acute poisoning are weak and irregular pulse, breathing difficulties, and general convulsions.

There are no clear evidence of nicotine being genotoxic or mutagenic. The well established carcinogenicity of tobacco smoke is mainly related to substances formed by the pyrolysis of tobacco. None of these occur in nicotine sublingual tablets.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Microcrystalline cellulose
Povidone (90F)
Methylcellulose
Silicified microcrystalline cellulose
Magnesium stearate
Lemon flavour
Aspartame
Flavour

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

Pack sizes
Cardboard box of 30, 90 and 100 sublingual tablets with a carry case and package insert/booklet.

The tablets will be packed in AL/AL blisters of 10 sublingual tablets.

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

MCNEIL HEALTHCARE (IRELAND)
Airton Road
Tallaght
Dublin 24

8 MARKETING AUTHORISATION NUMBER

PA 823/49/19

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 6th July 2007

10 DATE OF REVISION OF THE TEXT

April 2008