

Data Sheet

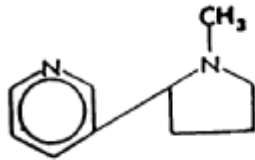
Nicorette® Microtab Classic

Sublingual Tablet containing 2mg nicotine

Presentation

NICORETTE Microtab contains nicotine, and is available as unflavoured sublingual tablets.

The chemical name for nicotine is (S)-3-(1-methyl-2-pyrrolidinyl)pyridine. The chemical structure is:



CAS 54-11-5

NICORETTE Microtab Classic (Unflavoured) 2mg contains 17.1mg nicotine betadex equivalent to nicotine 2mg. Nicotine is present in this product in the form of a complex with betadex (β -cyclodextrin). Complexation by betadex stabilises nicotine and modifies its release characteristics.

Uses

Actions

Pharmacotherapeutic group: Drug for treatment of nicotine dependence.

ATC code: N07B A01.

Nicotine is a natural alkaloid which has ganglion stimulating properties and produces a wide range of pharmacological actions.

The use of nicotine is widespread in the form of tobacco products, chronic use of which is causally linked to a variety of serious diseases. Many smokers develop a dependence due to an interaction of pharmacological, social and psychological factors.

Pharmacodynamics

NICORETTE Microtab is a treatment-aid in smoking cessation. Clinical studies have shown that nicotine replacement from nicotine containing

products can help people give up smoking by relief of abstinence symptoms associated with smoking cessation.

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.

Pharmacokinetics

Pharmacokinetic properties of Nicorette Microtab

The amount of nicotine absorbed from a nicotine sublingual tablet depends on the amount of nicotine released in the oral cavity and the amount that is swallowed. Most of the nicotine absorbed from a NICORETTE Microtab tablet is absorbed through the buccal mucosa. The absolute bioavailability of nicotine after sublingual administration of the tablet is approximately 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 NICORETTE Microtab sublingual tablet.

A maximum plasma concentration of about 7 ng/mL will be achieved after a single dose of a 4 mg tablet.

The therapeutic blood concentration, i.e. the blood concentration level that relieves craving, is individual, based on the patient's nicotine dependence.

The 2 mg strength of NICORETTE Microtab results in a plasma nicotine level of about 33% of normal smoking levels whereas a 4 mg tablet results in about a 66% level. Normal smoking level is defined as 20 cigarettes/day.

Steady-state trough nicotine plasma concentrations achieved after 10 hourly doses of one 2 mg tablet are about 10 ng/mL which is about 50% of normal smoking levels.

A study of ad libitum use of 2 mg NICORETTE Microtab gave nicotine plasma levels of 3.3-15.1 ng/mL (mean 7.6 ng/mL). The number of Microtab tablets used varied from 5 to 20/day depending on how much nicotine the individual needed. This variation was no more marked than that seen with normal smoking (9.15-45.9 ng/mL; mean 25.7 ng/mL).

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

Severe renal impairment would be expected to affect the clearance of nicotine and its metabolites. Raised nicotine levels have been seen in smoking patients undergoing haemodialysis.

The volume of distribution following IV administration of nicotine is about 2 to 3 L/kg and the half-life ranges from 2 to 3 hours. The major eliminating organ is the liver, and average plasma clearance is about 70 L/hour. 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.

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 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.

There are no differences in nicotine kinetics between men and women.

Clinical Trials

The clinical efficacy and safety of NICORETTE Microtab has been evaluated in several long-term studies. The two pivotal studies were double-blind, randomised, parallel group comparisons of NICORETTE Microtab with placebo, in which a total of 488 smokers who were motivated to quit received active treatment for up to six months. The dosage in highly dependent smokers (baseline score ≥ 7 on the Fagerström Tolerance Questionnaire (FTQ)) was two 2 mg tablets per hour, up to a maximum of 40 daily, whereas in low dependent smokers (baseline FTQ score < 7) the dosage was one 2 mg tablet per hour, with a maximum of twenty 2 mg tablets daily. After 3 months, the dosage was tapered off by 25% each month, with a total treatment duration of 6 months. All patients were followed up at 12 months.

The primary objective of these pivotal studies was to determine smoking cessation rates (from 2 weeks onwards) for NICORETTE Microtab compared with placebo.

Abstinence rates are shown below. Abstinence was higher on active treatment and this difference was significant up to 6 months.

Efficacy in completely abstinent subjects from week 2

Quit rates by treatment, (N=488 in 2 studies) (Report numbers 9720186 & 9720257)

GROUP	NUMBER OF PATIENTS	AT 3 WEEKS	AT 6 WEEKS	AT 3 MONTHS	AT 6 MONTHS	AT 12 MONTHS
NICORETTE MICROTAB	243	62-63%	48-50%	33-42%	20-33%	17-23%
PLACEBO	245	34-40%	23-29%	17-23%	11-18%	10-15%

In both studies NICORETTE Microtab significantly depressed the “urge to smoke”. The subjects who received active treatment gave it a higher acceptance rating than placebo with respect to helping craving relief, staying off cigarettes and being a good method to aid smoking cessation.

Indications

A treatment-aid to smoking cessation for the relief of tobacco withdrawal symptoms.

Dosage and Administration

NICORETTE Microtab should be placed under the tongue where it dissolves slowly, in about 30 minutes. It is important to emphasise to the patient that the tablet should not be swallowed but be allowed to dissolve under the tongue. During the first few days of treatment, irritation in the mouth and throat may be experienced. Nearly all patients will get used to this sensation after the first few days.

Advice and support normally improve the success rate.

Children

NICORETTE Microtab should not be administered to children under 12 years of age.

Adults and elderly

The initial dosage should be individualised on the basis of the patient’s nicotine dependence. Low dependent smokers should initially take one 2 mg tablet every 1 to 2 hours. Eight to twelve tablets per day will usually be adequate. Highly dependent smokers or patients who have failed to stop smoking with the 2mg tablet dose may use two 2mg tablets for each dose. No more than 40 sublingual tablets per day should be used.

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

Use of NICORETTE Microtab beyond 6 months is generally not recommended. Some ex-smokers may need longer treatment with the tablet to avoid returning to smoking.

Adolescents (12 to 18 years)

When deciding whether to recommend NRT an assessment should be made on the individual's nicotine dependence, motivation to quit and willingness to accept counselling. Counselling is considered to be vitally important in the effective treatment of tobacco dependence in this age group.

The initial dose is as for adults. Continue use for up to 8 weeks to break the habit of smoking, then gradually reduce the dose over a 4 week period. When daily use is 1-2 tablets, use should be stopped.

As data on use of NRT in this age group are limited, the recommended duration of treatment is 12 weeks. If longer treatment is required, advice should be sought from a healthcare professional.

Before a recommendation to extend treatment beyond 12 weeks is made the patient should be reassessed for commitment to quitting, expected benefit of continued treatment and maturity. Treatment should not be extended by more than a further 4 weeks.

Contraindications

NICORETTE Microtab should not be taken by non-tobacco users or patients with known hypersensitivity to nicotine or any of the other ingredients in the tablets.

Nicorette Microtab Classic (unflavoured) does not contain aspartame.

Use in children

Should not be administered to children under 12 years of age. (See DOSAGE AND ADMINISTRATION – Children).

Warnings and Precautions

Any risks that may be associated with NRT are substantially outweighed by the well established dangers of continued smoking.

Underlying cardiovascular disease

In stable cardiovascular disease NICORETTE Microtab presents a lesser hazard than continuing to smoke. However dependent smokers currently hospitalised as a result of myocardial infarction, severe dysrhythmia or cerebrovascular accident (CVA) and who are considered to be haemodynamically unstable should be encouraged to stop smoking with non-pharmacological interventions. If this fails, NICORETTE may be considered, but as data on safety in this patient group are limited, initiation should only be under medical supervision.

Diabetes mellitus

Patients with diabetes mellitus should be advised to monitor their blood sugar levels more closely than usual when NRT is initiated as catecholamines released by nicotine can affect carbohydrate metabolism.

GI disease

Swallowed nicotine may exacerbate symptoms in patients suffering from oesophagitis, gastritis or peptic ulcers and oral NRT preparations should be used with caution in these conditions. Ulcerative stomatitis has been reported.

NICORETTE Microtab should be avoided if oral or pharyngeal inflammation is present.

Renal or hepatic impairment

NICORETTE Microtab should be used 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

Nicotine, both from NRT and smoking, causes the release of catecholamines from the adrenal medulla. Therefore, NICORETTE Microtab should be used with caution in patients with uncontrolled hyperthyroidism or phaeochromocytoma.

Transferred dependence

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

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

Use in the elderly

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

Continued smoking while using NRT

Patients must be made aware that should they continue to smoke whilst using NICORETTE Microtab, they may experience increased adverse effects due to the increased levels of nicotine beyond those normally experienced with smoking or NICORETTE Microtab alone. Such adverse effects include cardiovascular effects (eg angina, rapid or irregular heart beats).

Carcinogenesis, mutagenesis, impairment of fertility

Literature reports indicate that nicotine is neither an initiator nor a tumour promoter in mice. There is inconclusive evidence to suggest that cotinine, an oxidised metabolite of nicotine, may be carcinogenic in rats.

Neither nicotine nor cotinine was mutagenic in the Ames Salmonella test.

Studies have shown a decrease of litter size in rats treated with nicotine during the time of fertilisation.

Use in pregnancy: Category D

Nicotine is harmful to the foetus. The harmful effects of cigarette smoking on maternal and foetal health are clearly established. Short-term exposure during the first trimester is unlikely to cause a hazard to the foetus.

NRT is not contraindicated in pregnancy. The decision to use NRT should be made on a risk-benefit assessment as early on in the pregnancy as possible with the aim of discontinuing use as soon as possible.

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.

Ideally smoking cessation during pregnancy should be achieved without NRT. However for women unable to quit on their own, NRT may be recommended to assist a quit attempt.

Nicotine passes to the foetus affecting breathing movements and has a dose-dependent effect on placental/foetal circulation. However the risk of using NRT to the foetus is lower than that expected with tobacco smoking, due to lower maximal plasma nicotine concentration and no additional exposure to polycyclic hydrocarbons and carbon monoxide.

Intermittent dosing products may be preferable as these usually provide a lower daily dose of nicotine than patches. However, patches may be preferred if the woman is suffering from nausea during pregnancy. If patches are used they should be removed before going to bed.

Use in lactation

NRT is not contraindicated in lactation. Nicotine from smoking and NRT is found in breast milk. However the amount of nicotine the infant is exposed to is relatively small and less hazardous than the second-hand smoke they would otherwise be exposed to.

Using intermittent dose NRT preparations, such as NICORETTE Chewing Gums, Microtab or Inhaler, may minimize the amount of nicotine in the breast milk as the time between administrations of NRT and feeding can be more easily prolonged. Women should breastfeed just before using the product

Interactions

Interactions with other Drugs

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.

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, clozapine and ropinirole.

The plasma concentration of other drugs metabolised in part by CYP1A2, for example imipramine, olanzapine, clomipramine, fluvoxamine and caffeine may also increase on cessation of smoking, although data to support this are lacking and the possible clinical significance of this effect is unknown.

Limited data indicate that the metabolism of flecainide and pentazocine may also be induced by smoking.

Adverse Reactions

NICORETTE Microtab may cause adverse reactions similar to those associated with nicotine administered by other means, such as gum, patch or inhaler and are dose dependent.

Most of the adverse events reported occur during the first 3 to 4 weeks after starting treatment. Many users may in the beginning of the treatment experience irritation in the mouth and throat. The adverse events are mainly due to the local or systemic pharmacological effects of nicotine, which are dose-dependent.

Frequency of the more common adverse reactions

INCIDENCE	BODY SYSTEM	ADVERSE REACTION
Common (>1/100)	CNS	Headache
	Gastrointestinal	Nausea, gastrointestinal discomfort, hiccups
	Respiratory	Coughing
	Local	Sore mouth or throat, dry mouth, burning sensation in the mouth
Less common (1/100 -1/1000)	Circulation	Palpitations
Rare (<1/1000)	Cardiovascular	Reversible atrial fibrillation

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

Overdosage

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

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

Overdosage with nicotine can occur if the patient has a very low pre-treatment nicotine intake or uses other forms of nicotine. The acute minimum lethal oral dose of nicotine in non-smokers is believed to be 40-60 mg.

Doses of nicotine that are tolerated by adult smokers during treatment may produce severe symptoms of poisoning in small children and may prove fatal. The lethal dose of nicotine in a small child is approximately 10-15 mg.

Management of overdose

If tablets are ingested, activated charcoal should be given as soon as possible. Contact the Poisons Information Centre (0800 764 766) for advice on treatment.

The administration of nicotine must be stopped immediately and the patient should be treated symptomatically. Activated charcoal reduces gastrointestinal absorption of nicotine.

Pharmaceutical Precautions

Shelf-life and Special Precautions for Storage

Nicorette Microtab Classic: 24 months stored at or below 25°C.

Medicine Classification

General Sale Medicine.

Package Quantities

Nicorette Microtab Classic 2mg: 30 and 100 pieces.

The sublingual tablets are packed in press through packages (blister packages) held together within a cardboard box.

Further Information

List of excipients

Nicorette Microtab Classic 2mg

Betadex
Crospovidone
Magnesium stearate
Colloidal silica

Name and Address

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Date of Preparation

28 August 2008