IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA0823/049/016
Case No: 2049368

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 10 mg/ml Nasal Spray

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 **18/04/2008**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Nicorette 10mg/ml Nasal Spray

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Nicotine 10 mg per ml. Each spray of 50 microlitres delivers 0.5 mg nicotine.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Nasal Spray, Solution. (Nasal Spray)
Colourless to pale yellow solution.

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 temporarily abstain from smoking.

It may be of particular use in heavily dependent smokers.

4.2 Posology and method of administration

Intra nasally.
Adults (including the elderly):

Smoking cessation
The spray should be administered according to the package insert. Counselling should also take place, if available. It is recommended the patient uses the spray when required, with a recommended level of one or two sprays to each nostril per hour. Each spray delivers 0.5 mg of nicotine, about half of which enters the circulation.

Dosage should not exceed two sprays to each nostril per hour for 16 hours per day (maximum 32mg per 24 hours).
The recommended period of treatment is 3 months as follows:

a) Over eight weeks dosage should be as required within the limits set out above.
b) After this period the patient reduces usage until after 4 or more weeks treatment is ended. It is suggested that after 2 weeks into this period, usage will have been reduced by half and usage be zero by the last day.

If the patient relapses, the physician may judge whether a further course is justified, coupled with full counselling.

Temporary Abstinence

During periods of temporary abstinence, Nicorette Nasal Spray can be used to relieve nicotine cravings and withdrawal symptoms. The recommended dose is one or two sprays into each nostril per hour – not more than 4 sprays (two into each nostril) should be used per hour and not more than a total of 64 sprays in a 24 hour period.

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

4.3 Contraindications

- Use in non-smokers.
- Use in persons hypersensitive to nicotine or any ingredient in Nicorette Nasal Spray.

4.4 Special warnings and precautions for use

Nicotine in any dose form is capable of inducing a dependence syndrome after chronic use and is highly toxic after acute use. However, dependence with Nicorette Nasal Spray is a rare side effect and is both less harmful and easier to break than smoking dependence.

Nicorette Nasal Spray should be used with caution in patients with cardiovascular disease, severe/moderate hepatic impairment, severe renal impairment, chronic nasal disorders, active and duodenal ulcers.

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

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

Nicorette Nasal Spray should be used with caution in patients with chronic nasal disorders (polyposis, vasomotor rhinitis, perennial rhinitis.)

A few cases of exacerbation of bronchospasm in patients with airways obstruction have been reported. Use of the spray in patients with hyperreactive airways is not recommended.

4.5 Interaction with other medicinal products and other forms of interaction

Smoking (but not nicotine) is associated with an 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 and for products with a narrow therapeutic window, e.g. theophylline, tacrine and clozapine.

The plasma concentration of other drugs metabolised in part by CYP1A2 e.g. imipramine, olanzapine, clonipramine and fluvoxamine 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 the metabolism of flecainide and pentazocine may also be induced by smoking.

4.6 Pregnancy and lactation

Pregnancy:
Nicotine passes freely 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 the use of nicotine replacement therapy. The risk of continued smoking may pose a greater hazard to the foetus as compared with the use of nicotine replacement therapy products in a supervised cessation programme. Use of Nicorette should only be initiated after advice from a physician.

Lactation:
Nicotine passes freely into breast milk in quantities that may affect the child even in therapeutic dose. Nicorette should therefore not be used during breast-feeding.

4.7 Effects on ability to drive and use machines

None.

4.8 Undesirable effects

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

Common (>1/100)

CNS:	Headache.
Gastrointestinal:	Nausea, GI discomfort, vomiting.
Respiratory:	Coughing.
Local:	Epistaxis, running nose, sneezing, watering eyes, throat irritation.

Less common (1/100-1/1000)

Circulation:	Palpitations.

Rare (<1/1000)

Cardiovascular:	Reversible atrial fibrillation.

Additionally an incidence greater than 1% compared with placebo was noted in clinical studies for the following: Sore nose, ear sensation, increased urination, tingling or burning sensation in the head, dyspepsia.

Symptoms such as dizziness, headache and sleeplessness may be related to withdrawal symptoms associated with smoking cessation. Increased incidence of aphthous ulcer may occur after smoking cessation. The causality is unclear.

4.9 Overdose

Excessive use of nicotine from either NRT and/or smoking might cause symptoms of an overdose. Symptoms of an overdose 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 overdose:
The administration of nicotine must be stopped immediately and the patient should be treated symptomatically. Tachycardia causing circulatory impairment may require treatment with a beta-blocker. Excitation and convulsions may be treated with diazepam. Mechanically assisted ventilation should be instituted if necessary.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

The pharmacology of nicotine is well known, its effects on many body systems being evident during smoking. Nicorette Nasal Spray allows rapid uptake of nicotine through the nasal membranes such that it can relieve the craving in people attempting to stop smoking.

5.2 Pharmacokinetic properties

Following administration of one dose of Nicorette Nasal Spray approximately 56% of the nicotine enters the systemic circulation.

The volume of distribution following i.v. administration of nicotine is approximately (2 to) 3 L/kg and half-life ranges from 1 to 2 hours. The major eliminating organ is the liver and average plasma clearance is about 1.2 L/min: 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 proteins binding of nicotine is <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 a significant effect on nicotine kinetics.

The primary urinary metabolites are cotinine (15% of the dose) and trans-3-hydroxycotinine (45% of the dose). Usually about 10% of nicotine is excreted unchanged in the urine. As much as 30% may be excreted in the urine with high urine flow rates and acidification below pH 5.

Plasma levels of nicotine obtained with Nicorette Nasal Spray rise rapidly, reaching a maximum level – mean after approximately 10-15 minutes.
The mean peak plasma level of nicotine - after steady-state is achieved – given 1 dose/hour, 2 doses/hour and 3 doses/hour are approximately 10, 19 and 28ng/ml respectively.

After repeated administration of the Nicorette Nasal Spray the AUC was significantly higher during the last dosing interval as compared to the first giving an accumulation ratio of 3:1. No dose-dependency has been shown for the doses 0.5mg and 1mg nicotine.

The therapeutic blood concentrations of nicotine, (i.e. the blood levels which relieve craving) are individually based on the patients nicotine dependence.

5.3 Preclinical safety data

None of relevance to the prescriber.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium Phosphate Dodecahydrate
Sodium Dihydrogen Phosphate Dihydrate
Anhydrous Citric Acid
Sodium Chloride
Polysorbate 80
NNS Aroma DZ-03226 (β-ionone)
Methyl Parahydroxybenzoate (E218)
Propyl Parahydroxybenzoate (E216)
Disodium Edetate
Purified Water

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

2 years.

6.4 Special precautions for storage

Store in the original package.

6.5 Nature and contents of container

Type III Ph. Eur., amber glass bottle with 50 microlitre metered spray pump, white PP nosepiece applicator with white polyoxymethylene nozzle and a white PP child resistant closure. Pack sizes: 10 ml.

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

See directions in Patient Information Leaflet. When priming the pump point it safely away.

7 MARKETING AUTHORISATION HOLDER

McNeil Healthcare (Ireland) Ltd.
Airton Road
Tallaght
Dublin 24

8 MARKETING AUTHORISATION NUMBER

PA 823/49/16

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10th November 1994
Date of last renewal: 2nd January 2007

10 DATE OF REVISION OF THE TEXT

April 2008