Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Nicorette 15mg Inhaler

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Nicotine 15mg per cartridge.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Inhalation cartridge for oromucosal use.

White to slightly coloured porous plugs in sealed, transparent plastic cartridges.

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

In smokers currently unable or not ready to stop smoking abruptly, Nicorette inhaler may also be used as part of a programme to reduce smoking prior to stopping completely.

In certain circumstances, Nicorette Inhaler may be used in combination with Nicorette Invisi 10mg and 15mg Transdermal Patch for the treatment of tobacco dependence as part of a stop smoking programme.

4.2 Posology and method of administration

Adults (including the elderly)

Dosage
Smoking Cessation
The frequency of use should depend on the previous smoking habit of the individual. Nicorette Inhaler should be used whenever the urge to smoke is felt, up to a maximum usage of 6 cartridges per day.

In the treatment of nicotine dependence, a course not exceeding three months is suggested, the patient stopping smoking completely at the start of the course.

Administration of nicotine should be stopped temporarily if any symptoms of nicotine excess occur. Nicotine intake should be decreased by lowering dosing frequency if nicotine excess symptoms persist (see Section 4.9).

a) For up to 8 weeks the patient uses not less than 3 and not more than 6 cartridges each day to relieve craving.
b) Over the following two weeks the aim is to reduce the number of cartridges used by half, over the next two weeks to reduce the number to zero by the last day.
c) If abstinence has not been achieved, further courses of treatment may be recommended, if it is considered that the patient would benefit.
d) Counselling and support from family, friends and health professionals can improve the chances of abstinence.

Temporary Abstinence
During periods of temporary abstinence, the patient should use the Inhaler when required to relieve nicotine cravings and withdrawal symptoms. No more than 6 cartridges should be used in a 24 hour period.

Gradual cessation

For smokers who are unwilling or unable to quit abruptly.
Use the inhaler whenever there is a strong urge to smoke in order to reduce the number of cigarettes smoked as far as possible and to refrain from smoking as long as possible.

The number of cartridges is variable and depends on the patients needs. Not more than 6 cartridges should be used per day.

If a reduction in number of cigarettes per day has not been achieved after 6 weeks, professional advice should be sought.

If the attempt to stop smoking completely has not been started within 6 months after the beginning of treatment, it is recommended to consult a healthcare professional.

Reduced tobacco consumption should lead to complete cessation of smoking. A quit attempt should be made as soon as the number of cigarettes has been reduced to a level whereby the smoker feels ready to quit completely, and then start as outlined for "smoking cessation" as given above.

Combination Therapy

It may sometimes be beneficial to utilize more than one form of NRT concurrently. For example, combination therapy could be used by heavy smokers (more than 20 cigarettes a day) or smokers who have relapsed with NRT monotherapy in the past, who experience breakthrough acute cravings or have difficulty controlling cravings for cigarettes using monotherapy. Hence, if required, the Nicorette Invisi Patch may be combined with the Nicorette Inhaler.

Step 1: The Nicorette Invisi 15mg Patch would be applied daily on waking for 16 hours and removed just before bedtime for a total of 8 weeks. The Nicorette Inhaler 15mg would be used *ad libitum* when the smoker feels an urge to smoke or in situations where he/she feels that breakthrough cravings may occur, up to a maximum of 6 cartridges per day.

Step 2: After the initial 8 weeks the lower dose Nicorette Invisi 10mg Patch should be used. The Nicorette Invisi 10mg Patch would be applied daily on waking for 16 hours and removed just before bedtime for a total of 4 weeks. The Nicorette Inhaler would be used *ad libitum* when the smoker feels an urge to smoke or in situations where he/she feels that breakthrough cravings may occur, up to a maximum of 6 cartridges per day.

Step 3: Use of the Nicorette Invisi Patch should be stopped after the 12 week treatment program. The Nicorette Inhaler can continue to be used for a further 3 months during which time the habits associated with smoking will be lost.

Recommended dosage

Dose regimen			Duration
Step 1	Nicorette Invisi Patch 15 mg	Nicorette Inhaler	First 8 weeks
Step 2	Nicorette Invisi Patch 10 mg	Nicorette Inhaler	Next 4 weeks
Step 3	No patch applied	Nicorette Inhaler	Next 3 months

Method of administration
The cartridge is inserted into the mouthpiece according to the instructions. The patient draws air into the mouth through the mouthpiece: there is a greater effort needed than with a cigarette. The patient may find deep drawing or short sucks on the mouthpiece most effective – patients soon find a favoured technique. Nicotine vapour passing through the mouth is absorbed by the buccal mucosa: little reaches the lungs. Each cartridge can be used for approximately eight 5-minute sessions, with each cartridge lasting approximately 40 minutes of intense use. After this the nicotine amounts released from the cartridge begin to fall away, such that the user rejects the cartridge and it is then that the nicotine amounts released from the cartridge begin to fall away, such that the user rejects the cartridge. The actual time that the cartridge is active depends on the intensity of use.

Concomitant disease
Only severe renal impairment would be expected to affect the clearance of nicotine or its metabolites from circulation. In patients smoking and undergoing 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. Patients with obstructive lung disease may find use of the Inhaler difficult. Nicotine gum, patch, microtab or nasal spray may be preferred in such cases.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
Use in non-smokers.

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

• 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.

If a child swallows, chews, or sucks on the nicotine cartridge (used as well as unused), there is a risk of poisoning in the child.

Transferred dependence: Transferred dependence can occur but is unusual and both less harmful and easier to break than smoking dependence.

Nicorette Inhaler should be used with caution in smokers with chronic throat diseases and bronchospastic disease.

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, ropinirole and clozapine.

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 is unknown.

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

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.

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 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 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 be avoided during breast-feeding.
Should smoking cessation not be achieved, use of the Nicorette Inhaler by breast feeding smokers should only be initiated after advice from a health care professional. Women should take Nicorette Inhaler just after having breastfed.Fertility
In females tobacco smoking delays time to conception, decreases in-vitro fertilization success rates, and significantly increases the risk of infertility. In males tobacco smoking reduces sperm production, increases oxidative stress, and DNA damage. Spermatozoa from smokers have reduced fertilizing capacity.

The specific contribution of nicotine to these effects in humans is unknown.

4.7 Effects on ability to drive and use machines

Nicorette Inhaler has no or negligible effects 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 aphthous ulceration or nasopharyngitis. In addition, and of clinical significance, nicotine cravings may result in profound urges to smoke.

Adverse Drug Reactions

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

Most of the undesirable effects reported by the subjects occur during the early phase of treatment. Irritation in the mouth and throat may be experienced, however most subjects adapt to this with ongoing use. About 40% of the users experienced mild local reactions such as cough and irritation in the mouth and throat.

Allergic reactions (including symptoms of anaphylaxis) can occur during use of Nicorette Inhaler.

Adverse reactions observed in patients treated with nicotine oral formulations during clinical trials and post-marketing experience are listed below by System Organ Class (SOC).
Frequencies are defined in accordance with current guidance, as: 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

BodySystem	**Incidence**	**Reportedadverseevent (PreferredTerm)**
Immune system disorders	Common	Hypersensitivity[a]
	Not known	Anaphylactic reaction
Psychiatric disorders	Uncommon	Abnormal dreams*
Nervous system disorders	Very common	Headache [a#]
	Common	Burning sensation [c]
	Common	Dysgeusia
	Common	Paraesthesia [a]
	Unknown	Seizure*****
Eye disorders	Not known	Blurred vision
	Not known	Lacrimation increased
Cardiac disorders	Uncommon	Palpitations [a]
	Uncommon	Tachycardia [a]
	Not known	Atrial fibrillation
Vascular disorders	Uncommon	Flushing [a]
	Uncommon	Hypertension [a]

Respiratory, thoracic and mediastinal disorders	Very common	Throat irritation**
	Common	Cough**
	Uncommon	Bronchospasm
	Uncommon	Dysphonia
	Uncommon	Dyspnoea [a]
	Uncommon	Nasal congestion
	Uncommon	Sneezing
	Uncommon	Throat tightness
Gastrointestinal disorders	Very common	Hiccups****
	Very common	Nausea [a]
	Common	Abdominal pain
	Common	Diarrhoea***
	Common	Dry mouth
	Common	Dyspepsia
	Common	Flatulence
	Common	Salivary hypersecretion
	Common	Stomatitis
	Common	Vomiting [a]
	Uncommon	Eructation
	Uncommon	Glossitis
	Uncommon	Oral mucosal blistering and exfoliation
	Uncommon	Paraesthesia oral***
	Rare	Dysphagia
	Rare	Hypoaesthesia oral***
	Rare	Retching
	Not known	Dry throat
	Not known	Gastrointestinal discomfort [a]
	Not known	Lip pain
Skin and subcutaneous disorder	Uncommon	Hyperhidrosis [a]
	Uncommon	Pruritus [a]

	Uncommon	Rash [a]
	Uncommon	Urticaria [a]
	Not known	Angioedema [a]
	Not known	Erythema [a]
Muscoskeletal and connective tissue disorders	Uncommon	Pain in jaw [b]
	Not known	Muscle tightness [b]
General disorders and administration site conditions	Common	Fatigue [a]
	Uncommon	Asthenia [a]
	Uncommon	Chest discomfort and pain
	Uncommon	Malaise

[a] Systemic effects; [b]Tightness of jaw and pain in jaw with nicotine gum formulation
[c] At the application site
*Identified only for formulations applied during the night
**Higher frequency observed in clinical studies with inhaler formulation.
***Reported the same or less frequently than placebo
**** Higher frequency observed in clinical studies with mouth spray formulation
# Although the frequency in the active group is less than that of the placebo group, the frequency in the specific formulation in which the PT was identified as a systemic ADR was greater in the active group than the placebo group.
***** 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 HPRA Pharmacovigilance, website: www.hpra.ie.

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. In extreme cases these symptoms may be followed by hypotension, rapid irregular pulse, breathing difficulties, prostration, circulation collapse and terminal 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
All nicotine intake should cease immediately and the patient should be treated symptomatically. If excessive amount of nicotine is swallowed, activated charcoal reduces the gastrointestinal absorption of nicotine. Tachycardia causing circulatory impairment may require treatment with a β blocker. Excitation and convulsions may be treated with diazepam. Artificial respiration with oxygen should be instituted if necessary.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drug for treatment of addiction.

ATC code: N07B A01

Nicorette Inhaler facilitates uptake of nicotine through the buccal mucosa into the venous circulation. The amount taken up alleviates the craving symptoms caused by the absence of nicotine from smoking.

5.2 Pharmacokinetic properties

Nicotine given iv has a volume of distribution of 2 to 3L/kg with half-life of 1-2 hours. Average plasma clearance is about 1-2L/min mainly in the liver. More than 20 metabolites are known, all less active than nicotine: cotinine, with a half life of 15-20 hours and concentrations ten times that of nicotine is the main one Plasma binding of nicotine below 5% means significant displacement of drugs or nicotine is unlikely. Nicotine is excreted in the urine principally as cotinine (15%), 3-hydroxycotinine (45%), nicotine (10%).

Most inhaled nicotine is absorbed via the buccal mucosa. Forced rapid inhalation over 20 minutes will remove up to 4mg of the nicotine from the cartridge. Uptake is slow and free of peaks resultant from cigarette smoking – about one-third that from smoking and equivalent to an hourly 2mg nicotine chewing gum.

Peak plasma levels occur within 15 minutes after the end of inhalation. Forced rapid inhalation for 20 minutes per hour for 12 hours achieved steady state levels of 20-25 ng/ml.

Ambient temperatures affects volatilisation of nicotine, the biologically available dose rising by 35% for each 10°C above 20°C. Use below 15°C is not recommended.

Because the pattern of use is decided by the patient up to a limit of 6 cartridges per day to relieve craving, therapeutic levels of nicotine are individual, dictated by the level of dependence.

5.3 Preclinical safety data

In vitro and in vivo genotoxicity testing of nicotine has yielded predominantly non- genotoxic results. Some positive findings from in vitro and in vivo genotoxicity tests have been reported but investigations using regulatory accepted assays and protocols have shown no evidence of genotoxic activity at therapeutic doses.

Animal experiments have shown that nicotine exposure results in decreased birthweight, decreased litter size and decreased survival of offspring.

Analysis of the results from long-term carcinogenicity assays data with nicotine or cotinine (a major nicotine metabolite) predominantly indicates that nicotine does not have any significant or relevant carcinogenic activity.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Levomenthol
Porous plug of polyethylene

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

There are no special storage conditions for this product

6.5 Nature and contents of container

Aluminium foil sealed plastic cartridges, to be used in a polypropylene mouthpiece.

Pack sizes: Packs containing 4 cartridges and a plastic mouthpiece.
Packs containing 20 cartridges and a plastic mouthpiece.

Not all pack sizes will be marketed.

6.6 Special precautions for disposal and other handling

1) Remove the Aluminum foil sealed tray and the mouthpiece from the carton box.
2) Peel back the foil from the tray. Pull the mouthpiece apart.
3) Insert the cartridge into the mouthpiece, whereby the seal of the inserted end of the cartridge is perforated.
4) Push the other part of the mouthpiece back into place over the cartridge. The product is now ready for use.

Grip the mouthpiece in the lips as air is inhaled, the nicotine is vaporised and absorbed in the mouth.

Disposal Instructions.
Because of residual nicotine, used cartridges may be a hazard to children, animals and fish and so should never be thrown away or left lying around. They should be kept in the case and disposed of in with household rubbish.

Cleaning the mouthpiece.
The empty mouthpiece should be rinsed in water several times a week. Nicorette Inhaler should be used when the patient has the urge for a cigarette or feels the onset of other withdrawal symptoms, up to a maximum of six cartridges per day.

The number, frequency, puffing/inhalation time and technique vary individually. Studies show that different inhalation techniques give similar effects: deep inhalation (the cigarette smokers way) or shallow puffing (the pipe smokers way). The amount of nicotine from a puff is less than that from a cigarette.

To compensate for less nicotine delivery from a puff, it is necessary to inhale more often than when smoking a cigarette, i.e. use the Nicorette Inhaler for longer periods at a time. After using a few cartridges the patient will have found a method that suits him/her and gives the best effect.

This product works best at room temperature. In cold conditions the nicotine evaporates less readily and it will be necessary to inhale more frequently, whilst in warm conditions nicotine will evaporate more readily and inhalation should be less frequent to avoid overdose.

7 MARKETING AUTHORISATION HOLDER

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