Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Nicorette Fruit 4 mg Lozenges

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each lozenge contains 4 mg nicotine (as nicotine resinate).
Excipients with known effects:
Polysorbate 80: 0.10mg/lozenge
Sulphites (0.000096 mg per lozenge).
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Compressed lozenge (lozenge)

An oval, white to off-white tablet imprinted with an "n" on one side and "4" on the other side.

The size of the lozenge is about 14 x 9 x 7mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Nicorette Fruit 4 mg Lozenges are to be used for the treatment of tobacco dependence by relief of nicotine withdrawal symptoms and cravings in smokers 18 years and above. Permanent cessation of tobacco use is the eventual objective.

Nicorette Fruit 4 mg Lozenges should preferably be used in conjunction with a behavioural support programme.

4.2 Posology and method of administration

Posology
Selecting the strength of lozenge to be used will depend on the smoking habits of the individual.

Adults
Nicorette Fruit 4 mg Lozenges are suitable for
smokers with high nicotine dependency e.g. those smoking their first cigarette of the day within 30 minutes of waking up or those who smoke more than 20 cigarettes per day.
Lozenges should not be used for more than 9 months. If users still feel the need for treatment, a healthcare professional should be consulted.
Behavioural therapy advice and support will normally improve the success rate.

Abrupt cessation of smoking:
The patient should make every effort to stop smoking completely during treatment with Nicorette Fruit Lozenges.

The lozenges should be used whenever there is an urge to smoke.
Sufficient lozenges should be used each day and most smokers usually require 8 to 12, not to exceed 15 lozenges.

The duration of treatment is individual, but up to six weeks treatment is recommended to break the habit of smoking. The nicotine dose should then be gradually reduced, by decreasing the total number of lozenges used per day. The treatment should be stopped, when the daily consumption is down to 1-2 lozenges.

Use a lozenge whenever there is an urge to smoke to maintain complete abstinence from smoking. In the event of sudden cravings any spare lozenges should be retained and used whenever there is a craving or an urge to smoke.

Gradual cessation through progressive reduction in smoking:
For smokers who are unwilling or unable to quit abruptly.

Use a lozenge between smoking episodes to manage the urge to smoke, to prolong smoke-free intervals and with the intention to reduce smoking as much possible.

The number of lozenges a day is variable and depends on the patients needs. Nonetheless it should not exceed 15 lozenges per day.

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

Reduced tobacco consumption should lead to complete cessation of smoking. A quit attempt should be made as soon as the smoker feels ready, but not later than 6 months after start of treatment. When the number of cigarettes has been reduced to a level from which the user feels able to quit completely, then the schedule for "abrupt cessation" as given above should be started.
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.

Paediatric population
Nicorette Fruit 4 mg Lozenges should only be used by adolescents (12-17 years inclusive) with advice from a healthcare professional. Nicorette Fruit Lozenges are not to be used by children below the age of 12.

The safety and efficacy of Nicorette Fruit 4 mg Lozenges in children and adolescents have not been investigated.

Method of administration
Oromucosal use.

One lozenge should be placed in the mouth and allowed to dissolve. Periodically, the lozenge should be moved from one side of the mouth to the other, and repeated, until the lozenge is completely dissolved (approximately 16-19 minutes). The lozenge should not be chewed or swallowed whole.
Users should not eat or drink while a lozenge is in the mouth.

4.3 Contraindications

- Hypersensitivity to nicotine or to any of the other 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 usually outweigh any risk 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 Fruit 4 mg Lozenge 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 reduction 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:* Swallowed nicotine may exacerbate symptoms in patients suffering from oesophagitis, gastric or peptic ulcers and oral 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).

Lozenges can represent a choking hazard. Use with caution in individuals with aspiration and swallowing problems

Paediatric population
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.

Stopping Smoking: Polycyclic aromatic hydrocarbons in tobacco smoke induce the metabolism of drugs metabolized by CYP 1A2 (and possibly by CYP 1A1). When a smoker stops smoking, this may result in a 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.

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

Excipients:
This medicine contains less than 1 mmol sodium (23 mg) per lozenge, that is to say essentially 'sodium-free'. This medicine also contains a small amount of sulphites, coming from the flavour, which may rarely cause severe hypersensitivity reactions and bronchospasm.
This medicine contains polysorbate which can cause allergic reactions.

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 increase 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 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 effect on the circulation is dose-dependent. Therefore, the pregnant smoker should always be advised to stop smoking completely without use of nicotine replacement therapy. The risk of continued smoking may pose greater hazard to the foetus as compared with the use of nicotine replacement products in a supervised smoking cessation programme. Use of this medicine by the pregnant smoker should only be initiated after advice from a healthcare professional.

Breast-feeding
Nicotine passes freely into breast milk in quantities which may affect the child, even at therapeutic doses. The Nicorette Fruit Lozenge should therefore be avoided during breast-feeding. Should smoking cessation not be achieved, use of the Nicorette Fruit Lozenge by breast feeding smokers should only be initiated after advice from a healthcare professional. Where nicotine replacement therapy is used whilst breast-feeding, the Nicorette Fruit Lozenges should be taken just after breastfeeding and not during the two hours before breast-feeding.

Fertility

Smoking increases the risk for infertility in women and men. In vitro studies have shown that nicotine can adversely affect human sperm quality. In rats, impaired sperm quality and reduced fertility have been shown (see section 5.3).

4.7 Effects on ability to drive and use machines

Nicorette Fruit 4 mg Lozenge has no or negligible influence on the ability to drive and use machines. However, nicotine replacement users should be aware that cessation of smoking may cause changes in behaviour.

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.

The Nicorette Fruit Lozenge may cause adverse reactions similar to those associated with nicotine given by other means.

Most of the undesirable effects reported by the subjects occur during the early phase of treatment and are mainly dose dependent.

Irritation in the mouth and throat may be experienced, however most subjects adapt to this with ongoing use.
Allergic reactions (including symptoms of anaphylaxis) occur rarely during use of Nicorette Fruit Lozenge.

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.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness:
very common (≥1/10), *common* (≥1/100 to <1/10), *uncommon* (≥1/1,000 to <1/100),
rare (≥1/10,000, <1/1,000), *very rare* (<1/10,000), not known (cannot be estimated from the available data).

System Organ Class	**Reported adverse reactions**
Immune System Disorders	
Common	Hypersensitivity
Not known	Allergic reactions including angioedema and anaphylaxis
Psychiatric disorders	
Uncommon	Abnormal dreams
Nervous system disorders	
Very common	Headache
Common	Dysgeusia, paraesthesia
Unknown	Seizure*
Eye disorders	
Not known	Blurred vision, lacrimation increased
Cardiac Disorders	
Uncommon	Palpitations, tachycardia, atrial fibrillation
Vascular disorders	
Uncommon	Flushing, hypertension
Respiratory, thoracic and mediastinal disorders	
Very common	Cough, hiccups, throat irritation
Uncommon	Bronchospasm, dysphonia, dyspnoea, nasal congestion, oropharyngeal pain, sneezing, throat tightness
Gastrointestinal disorders	
Very common	Nausea, mouth/throat and tongue irritation
Common	Abdominal pain, dry mouth, diarrhea, dyspepsia, flatulence, salivary hypersecretion, stomatitis, vomiting, heartburn
Uncommon	Eructation, glossitis, oral mucosal blistering and exfoliation,

	paresthesia 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 know	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 to HPRA Pharmacovigilance, website: www.hpra.ie.

4.9 Overdose

The acute minimum lethal oral dose of nicotine in man is believed to be 40 to 60 mg.
When used as directed symptoms of overdose with nicotine may occur in patients with low pre-treatment nicotine intake or if other sources of nicotine are used concomitantly.

Paediatric population
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.

Symptoms
Symptoms of overdose are those of acute nicotine poisoning and include nausea, vomiting, increased salivation, abdominal pain, diarrhea, 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 terminal convulsions.

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drug used in nicotine dependence.
ATC Code: N07B A01
(Smoking cessation: N07BA, nicotine 01.)

Nicotine, the main alkaloid in tobacco products and a naturally occurring autonomic substance, is an agonist at nicotine receptors in the peripheral and central nervous system and has pronounced CNS and cardiovascular effects. When consumed in tobacco products, it has been shown to be addictive and upon cessation craving and withdrawal symptoms occur. These craving and withdrawal symptoms include urge to smoke, depressed mood, insomnia, irritability, frustration or anger, anxiety, difficulty in concentrating, restlessness and increased appetite or weight gain. The lozenges replace some of the nicotine provided by tobacco and help reduce the severity of craving and withdrawal symptoms.

Cessation rates for reference Nicotine Lozenges from clinical studies have been reported as follows:

	Nicotine Lozenge 2 mg			Nicotine Lozenge 4 mg		
Treatment duration at	Active	Placebo	Odds ratios, adjusted	Active	Placebo	Odds ratios, adjusted for centre effects

			for centre effects			
6-week	46.0%	29.7%	2.10	48.7%	20.8%	3.69
6-month	24.2%	14.4%	1.96	23.6%	10.2%	2.76

A study including Nicorette 4 mg lozenges measured relief in urges to smoke (i.e. craving relief) in 97 subjects. 48% of subjects of the study experienced craving relief 2 mins after placing Nicorette 4 mg Lozenge in the mouth, 76% after 5 mins and after 1h, 79% of the subjects still felt either no or very light urges to smoke.

5.2 Pharmacokinetic properties

Absorption
Nicorette Fruit 4 mg Lozenges completely dissolve in the oral cavity, and the entire amount of nicotine contained in the lozenge becomes available for buccal absorption or ingestion (swallowing).
Complete dissolution of Nicorette Fruit 4 mg Lozenge is typically achieved in 16-19 minutes. The peak plasma concentration of nicotine achieved after a single dose is approximately 8 ng/ml for a Nicorette Fruit 4 mg Lozenge. Ingestion of Nicorette Fruit 4 mg Lozenges not following dosing instructions (chewed, retained in the mouth and swallowed; chewed and immediately swallowed) gives a slower and a somewhat reduced absorption of nicotine.

Distribution
As the plasma protein binding of nicotine is low (4.9% - 20%), the volume of distribution of nicotine is large (2.5 l/kg). The distribution of nicotine to tissue is pH dependent, with the highest concentrations of nicotine found in the brain, stomach, kidney and liver.

Biotransformation
Nicotine is extensively metabolized to a number of metabolites, all of which are less active than the parent compound. The metabolism of nicotine primarily occurs in the liver, but also in the lung and kidney. Nicotine is metabolized primarily to cotinine but is also metabolized to nicotine N-oxide. Cotinine has a half-life of 15-20 hours and its blood levels are 10 times higher than for nicotine. Cotinine is further oxidized to trans-3-hydroxycotinine, which is the most abundant metabolite of nicotine in the urine. Both nicotine and cotinine undergo glucuronidation.

Elimination
The elimination half-life of nicotine is approximately 2 hours (range 1 - 4 hours). Total clearance for nicotine ranges from approximately 62 to 89 l/hr. Non-renal clearance for nicotine is estimated to be about 75% of total clearance. Nicotine and its metabolites are excreted almost exclusively in the urine. The renal excretion of unchanged nicotine is highly dependent on urinary pH, with greater excretion occurring at acidic pH.

5.3 Preclinical safety data

The general toxicity of nicotine is well known and taken into account in the recommended posology. Nicotinee was not mutagenic in appropriate assays. The results of carcinogenicity assays did not provide any clear evidence of a tumorigenic effect of nicotine. In studies in pregnant animals, nicotine showed maternal toxicity, and consequential mild fetal toxicity. Additional effects included pre- and postnatal growth retardation and delays and changes in postnatal CNS development. Studies in female rodents have shown that nicotine can decrease the number of oocytes in the fallopian tubes, decrease the concentration of serum estradiol, and result in a number of changes to the ovary and uterus. Studies in male rats have shown that nicotine can decrease testis weight, cause a reversible decrease in Sertoli cell numbers with impairment of spermatogenesis, and result in a variety of changes in the epididymis and vas deferens.
Effects were only noted following exposure to nicotine at levels in excess of those which will result from recommended use of Nicorette lozenges.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core
Mannitol (E421)
Xanthan gum
Tutti Frutti Flavour (contains traces of sulphites)
Gum Arabic (E414)
Sodium carbonate anhydrous (E500) (i)
Sucralose (E955)
Acesulfame potassium (E950)
Magnesium stearate (E470b)

Coating
Hypromellose (E464)
Tutti Frutti Flavour
Titanium dioxide (E171)
Sucralose (E955)
Microcrystalline Cellulose (E460)
Potassium aluminium silictate (E555)
Acesulfame potassium (E950)
Polysorbate 80

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Polypropylene container: 3 years.
Cardboard box: 3 years. Use within 3 months after removing the overwrap.

6.4 Special precautions for storage

Polypropylene container: Store the lozenges in the original container in order to protect from moisture.
Cardboard box: Store the lozenges in the original container in order to protect from moisture

6.5 Nature and contents of container

Polypropylene container with silica gel desiccant ("Flip pack") containing 20 lozenges
Pack Sizes: 20 (1x20), 80 (4x20) and 160 (8x20) lozenges.

Cardboard box of 40 lozenges. Pack sizes: 40 (1x40), 80 (2x40) or 160 (4x40).
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Remaining unused medicinal product may have harmful effects if reaching the aquatic environment.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

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