Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Niquitin Minis Cherry Flavour 4.0mg Compressed Lozenges

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each lozenge contains 4 mg nicotine (as nicotine resinate)

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Compressed Lozenge

White to off white oval lozenge of length 10 mm; width 5 mm; thickness 5 mm with convex surfaces; one surface bearing a debossed “T” logo.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Niquitin Minis are to be used for the treatment of tobacco dependence by relief of nicotine withdrawal symptoms including cravings during a quit attempt. (see section 5.1). Permanent cessation of tobacco use is the eventual objective.

Niquitin Minis should preferably be used in conjunction with a behavioural support programme.

4.2 Posology and method of administration

Posology

Users should make every effort to stop smoking completely during treatment with Niquitin Minis.

Adults (18 years and over)

The strength of mini lozenge to be used will depend on the smoking habits of the individual.
Niquitin Minis 4 mg Lozenges are suitable for smokers who smoke 20 cigarettes or more a day.

Behavioural therapy advice and support will normally improve the success rate.

Use the mini lozenges whenever there is an urge to smoke.
Sufficient lozenges should be used each day, usually 8−12, up to a maximum of 15.

Continue use for up to 6 weeks to break the habit of smoking, then gradually reduce lozenge use. When daily use is 1-2 lozenges, use should be stopped.

To help stay smoke free after treatment, users may take a lozenge in situations when they are strongly tempted to smoke.

Those who use lozenges beyond 9 months are recommended to seek additional help and advice from a healthcare professional.

Paediatric population

Adolescents (12-17 years inclusive) should only use Niquitin Minis with advice from a physician.

Niquitin Minis are contraindicated in children under 12 years of age.

Method of administration

For oromucosal use. One mini 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 10 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 any of the excipients listed in section 6.1.
- Children under the age of 12 years.
- Non-smokers.

4.4 Special warnings and precautions for use

The risks associated with the use of nicotine replacement therapy (NRT) are substantially outweighed in virtually all circumstances by the well established dangers of continued smoking.

Dependent smokers with a recent myocardial infarction, unstable or worsening angina including Prinzmetal's angina, severe cardiac arrhythmias, uncontrolled hypertension or recent cerebrovascular accident should be encouraged to stop smoking with non-pharmacological interventions (such as counselling). If this fails, Niquitin Minis 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 NRT is initiated as catecholamines released by nicotine can affect carbohydrate metabolism.

Allergic reactions: susceptibility to angioedema and urticaria.

A risk-benefit assessment should be made by an appropriate healthcare professional for patients with the following conditions:

- 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. Ulcerative stomatitis has been reported.

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.

Stopping smoking: Polycyclic aromatic hydrocarbons in tobacco smoke induce the metabolism of drugs catalysed by CYP 1A2 (and possibly by CYP 1A1). When a smoker stops 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 rare and is both less harmful and easier to break than smoking dependence.

During a quit attempt users should not interchange Niquitin Minis Lozenges with nicotine gums since pharmacokinetic data indicate a higher availability of nicotine from Niquitin Minis Lozenges in comparison to the gum.

4.5 Interaction with other medicinal products and other forms of interaction

No clinically relevant interactions between nicotine replacement therapy and other medicinal products have definitely been established, however nicotine may possibly enhance the haemodynamic effects of adenosine.

4.6 Fertility, pregnancy and lactation

Fertility

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. However, similar effects have not been reported to occur in humans.
See section 5.3.

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.

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

However, as nicotine passes to the foetus affecting breathing movements and has a dose dependent effect on placental/foetal circulation, the decision to use NRT should be made as early on in the pregnancy as possible. The aim should be to use NRT for only 2-3 months. Intermittent dose forms are preferable because of the potential for nicotine-free periods, but patches may be necessary if there is significant nausea and/or vomiting. If patches are used they should, if possible, be removed at night, when the foetus would not normally be exposed to nicotine

Breast-feeding

Nicotine from smoking and NRT is found in breast milk. However the amount of nicotine the infant is exposed to from NRT is relatively small and less hazardous than the second-hand smoke they would otherwise be exposed to.

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

Using intermittent dose NRT preparations may minimize the amount of nicotine in the breast milk as the time between administrations of NRT and feeding can be made as long as possible. Women should take breast-feeding hours into account before they take the product.

4.7 Effects on ability to drive and use machines

Niquitin Minis have no or negligible influence on the ability to drive and use machines. However, users of nicotine replacement products should be aware that smoking cessation can cause behavioural changes.

4.8 Undesirable effects

NRT can cause adverse reactions similar to those associated with nicotine administered in other ways, including smoking. These may be attributed to the pharmacological effects of nicotine, some of which are dose dependent. At recommended doses Niquitin Minis have not been found to cause any serious adverse reactions. Excessive consumption of Niquitin Minis by those who have not been in the habit of inhaling tobacco smoke could possibly lead to nausea, faintness or headaches.

Certain symptoms which have been reported such as depression, irritability, anxiety, increased appetite and insomnia may be related to withdrawal symptoms associated with smoking cessation. Subjects quitting smoking by any means could expect to suffer from headache, dizziness, sleep disturbance, increased coughing or a cold.

Adverse reactions are listed below by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000) and very rare (<1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

System organ class and frequency	**Adverse reaction**
Immune system disorders *Very rare*	Anaphylactic reactions
Psychiatric disorders *Common* *Uncommon*	Irritability, anxiety, sleep disorders including abnormal dreams Nervousness, depression
Nervous system disorders *Common*	Dizziness, headaches
Cardiac disorders *Uncommon*	Palpitations, heart rate increased
Respiratory, thoracic and mediastinal disorders *Common*	Cough, sore throat
Gastrointestinal disorders *Very common* *Common*	Nausea, mouth, throat and tongue irritation Vomiting, diarrhoea, gastro-intestinal discomfort, flatulence, hiccups, heartburn, dyspepsia
Skin and subcutaneous tissue disorders *Uncommon*	Rash
General disorders and administration site conditions *Uncommon*	Fatigue, malaise, chest pain

Paediatric population (12-17 years inclusive)

There are no specific adverse event data for this population. However, the frequency, type and severity of adverse reactions in adolescents are expected to be the same as in adults,based upon a the pharmacokinetic study demonstrating a similar pharmacokinetic profile in the adolescent age group compared to adults.

4.9 Overdose

Symptoms: The minimum lethal dose of nicotine in a non-tolerant man has been estimated to be 40 to 60 mg. Even small quantities of nicotine may be dangerous in children and may prove fatal. Suspected nicotine poisoning in a child should be considered a medical emergency and treated immediately. Symptoms of acute nicotine poisoning 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 or weak or irregular pulse, breathing difficulties, prostration, circulatory collapse and terminal convulsions.

Management: All nicotine intake should cease immediately and the patient should be treated symptomatically. Artificial respiration with oxygen should be instituted if necessary. Activated charcoal reduces the gastro-intestinal absorption of nicotine.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in nicotine dependence.
ATC Code: N07B A01

Mechanism of action

Nicotine 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 abstinence is linked to craving and withdrawal symptoms. 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. Cravings and other symptoms of nicotine withdrawal are at their most intense during the first few weeks of a quit attempt, diminishing thereafter. The lozenges replace some of the nicotine provided by tobacco and clinical studies measuring intensity of cravings and other withdrawal symptoms have been shown to alleviate these symptoms when they are at their most intense.

5.2 Pharmacokinetic properties

Absorption

Niquitin Minis dissolve completely in the oral cavity, and the entire amount of nicotine contained in the lozenge becomes available for buccal absorption or ingestion (swallowing). The complete dissolution of Niquitin Minis is typically achieved in 10 minutes. The mean peak plasma concentration of nicotine achieved after single 4 mg dose is approximately 9.1 ng/ml.

Distribution

As the plasma protein binding of nicotine is low (4.9%), 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 metabolised 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 metabolised primarily to cotinine but is also metabolised to nicotine N′-oxide. Cotinine has a half-life of 15-20 hours and its blood levels are 10 times higher than nicotine. Cotinine is further oxidised 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. Nicotine 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 foetal 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 Niquitin Minis.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E421)
Sodium alginate (E401)
Xanthan gum (E415)
Potassium bicarbonate (E501)
Calcium polycarbophil
Sodium carbonate anhydrous (E500)
Acesulfame potassium (E950)
Taste Masking Flavour
Cherry Flavour
Magnesium Stereate (E470b)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 30°C. Store in the original container in order to protect the product from moisture.

6.5 Nature and contents of container

Child resistant polypropylene tablet container incorporating a molecular sieve desiccant (sodium aluminosilicate) containing 20 lozenges.

Packs may contain 20 lozenges or 3 containers of 20 lozenges (60 lozenges).
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Chefaro Ireland DAC,
Treasury Building,
Lower Grand Canal
Street,
Dublin 2,
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1186/018/015

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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