Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

NiQuitin 4 mg Lozenge

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each lozenge contains 4 mg nicotine (as nicotine resinate).

Excipients with known effect: Aspartame (E951) 6 mg, Mannitol (E421) 1027 mg and Sodium 17 mg

For the full list of excipients see Section 6.1.

3 PHARMACEUTICAL FORM

Compressed lozenge

White, round compressed lozenge of 16 mm with convex surfaces, debossed NL4 on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

NiQuitin Lozenges are indicated for the relief of nicotine withdrawal symptoms including cravings associated with smoking cessation. NiQuitin Lozenges should preferably be used in conjunction with a behavioural support programme.

NiQuitin Lozenges are indicated in adults and adolescents aged 12 years and over.

4.2 Posology and method of administration

Posology

Adults (18 years and over)

NiQuitin 4 mg Lozenges are suitable for smokers who have their first cigarette of the day within 30 minutes of waking up.

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

Abrupt cessation of smoking:

Users should make every effort to stop smoking completely during treatment with NiQuitin Lozenges.

Recommended treatment schedule:

Step 1 **Weeks 1 to 6**	**Step 2** **Weeks 7 to 9**	**Step 3** **Weeks 10 to 12**
Initial treatment period	Step down treatment period	Step down treatment period
1 lozenge every 1 to 2 hours	1 lozenge every 2 to 4 hours	1 lozenge every 4 to 8 hours

During weeks 1 to 6 it is recommended that users take a minimum of 9 lozenges per day. Users should not exceed 15 lozenges per day.

To help stay smoke free beyond 12 weeks, users may take 1-2 lozenges per day only on occasions when they are strongly tempted to smoke.

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

Paediatric population

Adolescents (12-17 years) should follow the schedule of treatment for abrupt cessation of smoking as given above, but as data are limited, duration of Nicotine Replacement Therapy (NRT) in this age group is restricted to 12 weeks. If longer treatment is required, or where adolescents are unwilling or unable to quit smoking abruptly, advice from a healthcare professional should be sought.

NiQuitin Lozenges are contraindicated in children under 12 years of age.

Method of administration

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 20 – 30 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 the active substance or to any of the excipients listed in section 6.1.

NiQuitin lozenges should not be used by:
- children under the age of 12 years;
- non-smokers;

4.4 Special warnings and precautions for use

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

Dependent smokers with a recent myocardial infarction, severe cardiac arrhythmias, unstable or worsening angina including Prinzmetal`s angina, uncontrolled hypertension or recent cerebrovascular accident should be encouraged to stop smoking with non-pharmacological interventions (such as counseling). If this fails, NiQuitin Lozenges may be considered, but as data on safety in this patient group are limited, initiation should only be under medical supervision. If there is a clinically significant increase in cardiovascular or other effects attributable to nicotine, the lozenge dose should be reduced or discontinued.

*Diabetes**:*** Blood glucose levels may be more variable when stopping smoking, with or without NRT as catecholamines released by nicotine can affect carbohydrate metabolism, so it is important for diabetics to monitor their blood glucose levels more closely than usual while using this product.

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.
- *GI disease**:*** Swallowing of nicotine may exacerbate symptoms in persons suffering from active oesophagitis, oral or pharyngeal inflammation, gastritis, gastric ulcer or peptic ulcer and oral NRT preparations should be used with caution in these conditions. Ulcerative stomatitis has been reported.
- *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.

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.

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

Phenylketonuria: NiQuitin Lozenges are sugar free, but do contain aspartame which metabolises to phenylalanine, which is of relevance for those with phenylketonuria.

Mannitol: May have a mild laxative effect**.**

Sodium content: This medicinal product contains less than 1 mmol (23 mg) per lozenge that is to say essentially sodium-free.

During a quit attempt users should not interchange NiQuitin Lozenges with other nicotine oral dosage forms since pharmacokinetic data indicate a higher availability of nicotine from NiQuitin Lozenges in comparison to nicotine gum.

4.5 Interaction with other medicinal products and other forms of interactions

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. Smoking cessation itself may require the adjustment of some drug therapy.

4.6 Fertility, pregnancy and lactation

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 fetus 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 fetus affecting breathing movements and has a dose dependent effect on placental/fetal 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 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.

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 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.

Using intermittent dose NRT preparations, compared with patches, 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 try to breastfeed just before they take the product.

Fertility

There are no human data on the effects of nicotine on fertility. In animal studies, nicotine has been shown to adversely affect both the male and female reproductive systems (see section 5.3). The clinical relevance of such effects on fertility are unknown.

4.7 Effects on ability to drive and use machines

NiQuitin Lozenges 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, which are dose dependent. At recommended doses, NiQuitin Lozenges have not been found to cause any serious adverse events. Excessive consumption of NiQuitin Lozenges 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 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, 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).

System Organ Class and	**Adverse Reaction/Event**
Immune System Disorders *Very rare* *Unknown*	 anaphylactic reactions hypersensitivity
Blood and lymphatic system disorders *Uncommon*	 gingival bleeding; nosebleed
Psychiatric disorders *Common Uncommon*	Insomnia***, anxiety, irritability, increased appetite, anger, aggravated anxiety, abnormal dreaming; abnormal hunger, mood
Nervous system disorders *Common Uncommon* *Not known*	Headache***, dizziness, localised numbness; parageusia, metallic taste, taste perversion *seizures, tremor
Cardiac disorders *Uncommon*	 aggravated palpitations, palpitations, tachycardia
Vascular disorders *Uncommon*	 vascular disorder, flushing, skin flushed
Respiratory, thoracic and mediastinal disorders *Common* *Uncommon* *Not known*	hiccups, coughing***laryngismus, aggravated asthma, lower respiratory tract infection, nasal irritation; throat irritation, nasal congestion dyspnoea
Gastrointestinal disorders *Very common Common*	 nausea vomiting, dyspepsia, heartburn, indigestion, mouth irritation, mouth ulceration, tongue ulceration, diarrhoea, belching, flatulence, dry mouth, constipation

Uncommon *Not known*	peptic ulcer, dysphagia, aggravated dyspepsia, gastroesophageal reflux, hiatus, hernia, oesophagitis, eructation, buccal mucosa borborygmus, dry lips, dry throat tongue disorder, tooth ache salivary hypersecretion
Skin and subcutaneous tissue disorders *Uncommon* *Not known*	 ulceration, borborygmus, dry lips, dry throat, erythema, itching, rash, skin reaction localized, increased sweating angioedema
Musculoskeletal, connective tissue and bone disorders *Uncommon*	 jaw pain
Renal and urinary disorders *Uncommon*	 nocturia
General disorders and administration site conditions *Uncommon* *Not known*	 overdose effect, pain, leg pain, oedema legs asthenia***, fatigue***, malaise***, influenza like illness***

*observed in users taking anti-convulsant therapy or with a history of epilepsy

**Individuals with a tendency to experience indigestion may suffer initially from minor degrees of indigestion or heartburn if the 4 mg dose is used - slower chewing in the case of gum or the use of the 2 mg dose (if necessary more frequently) will usually overcome this problem.

***These events may also be due to withdrawal symptoms following smoking cessation.

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 , Earlsfort Terrace , IRL - Dublin 2; Tel : +353 1 6764971 ; Fax : +353 l 6762517 . Website : www.hpra.ie ; e-mail: hprapharmacovigilance@hpra.ie

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 adults, based upon a pharmacokinetic study demonstrating a similar pharmacokinetic profile in the adolescent age group compared to adults.

4.9 Overdose

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

Signs and symptoms of an overdose from nicotine lozenges would be expected to be the same as those of acute nicotine poisoning including pallor, cold sweat, salivation, nausea, vomiting, abdominal pain, diarrhoea, headache, dizziness, disturbed hearing and vision, tremor, mental confusion and weakness. Prostration, hypotension, respiratory failure, rapid or weak or irregular pulse, circulatory collapse and convulsions (including terminal convulsions) may ensue with large overdoses.

Management

In the event of an overdose (e.g. too many lozenges ingested) the user should seek medical attention immediately. All nicotine intake should cease immediately and the patient 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: N07BA01

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. The lozenges replace some of the nicotine provided by tobacco and help reduce the severity of these nicotine craving and withdrawal symptoms.

5.2 Pharmacokinetic properties

Absorption

NiQuitin 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). The complete dissolution of NiQuitin Lozenge is typically achieved in 20-30 minutes. The peak plasma concentrations of nicotine achieved after a single dose are approximately 10.8 ng/ml. When dosed every 1.5 hours, the steady state peak and trough concentrations are 26.0 and 19.7 ng/ml respectively. Ingestion of NiQuitin Lozenges not following dosing instructions (chewed, retained in the mouth, and swallowed; chewed and immediately swallowed) does not result in faster or higher absorption, but a substantial amount of nicotine (80-93%) is still absorbed.

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 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. 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 fetal toxicity. Additional effects included pre- and postnatal growth retardation and delays and changes in postnatal CNS development.

Effects were only noted following exposure to nicotine at levels in excess of those which will result from recommended use of NiQuitin Lozenges.

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 ovaries 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 on fertility have not been established.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E421)
Sodium alginate (E401)
Xanthan gum (E415)
Potassium hydrogencarbonate (E501)
Polycarbophil calcium
Anhydrous sodium carbonate (E500i)
Aspartame (E951)
Magnesium stearate (E470b)
Menthol mint flavour (menthol, peppermint oil, maltodextrin, colloidal anhydrous silica)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

18 months.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container

Clear or opaque Polyvinyl Chloride/Polyethylene/Polyvinylidene Chloride blisters in packs of 12, 36 and 72.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Chefaro Ireland DAC
The Sharp Building
Hogan Place
Dublin 2
Ireland

8 MARKETING AUTHORISATION NUMBER

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 31 May 1999
Date of last renewal: 26 April 2007

10 DATE OF REVISION OF THE TEXT

July 2021