SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

NiQuitin 2 mg Lozenges

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each lozenge contains 2 mg nicotine (as nicotine resinate). For excipients see Section 6.1.

3 PHARMACEUTICAL FORM

Lozenge

White, round lozenge with convex surfaces, debossed NL2 on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

NiQuitin Lozenges relieve and/or prevent craving and nicotine withdrawal symptoms associated with tobacco dependence. They are indicated to aid smokers wishing to quit or reduce prior to quitting, to assist smokers who are unwilling or unable to smoke, and as a safer alternative to smoking for smokers and those around them.

NiQuitin Lozenges are indicated in pregnant and lactating women making a quit attempt.

NiQuitin Lozenges should preferably be used in conjunction with a behavioral support programme.

4.2 Posology and method of administration

Directions for use:

NiQuitin 2 mg Lozenges are suitable for smokers who have their first cigarette of the day more than 30 minutes after waking up.

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.

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

Adults (18 years and over):

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 have quit smoking but are having difficulty discontinuing using the lozenges are recommended to seek additional help and advice from a healthcare professional.

Gradual cessation of smoking:

For smokers who are unwilling or unable to quit abruptly.
Use a lozenge 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 lozenges a day is variable and depends on the patients needs.
Nonetheless it should not exceed 15 lozenges per day.
If a reduction in cigarette consumption has not been achieved after 6 weeks of treatment, a healthcare professional should be consulted.

Reduced tobacco consumption should lead to complete cessation of smoking. This should be attempted as soon as possible. When the number of cigarettes has been reduced to a level from which the user feels able to quit completely, then start on the schedule for “abrupt cessation” as given above.
If an 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.

Reduction in smoking:

For smokers who wish to cut down with no immediate plans to quit.

Use a lozenge 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. Users should be encouraged to stop smoking completely as soon as 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 users are still feeling the need to use the lozenges on a regular basis 6 months after the start of treatment and have still been unable to undertake a permanent quit attempt, then it is recommended to seek additional help and advice from a healthcare professional.

Temporary abstinence:

Use a lozenge every 1-2 hours to control troublesome withdrawal symptoms including cravings. Users should not take more than 15 lozenges per day.

Users should be encouraged to stop smoking completely as soon as possible.
If users are still feeling the need to use lozenges on a regular basis 6 months after the start of treatment and have still been unable to undertake a permanent quit attempt, then it is recommended to seek additional help and advice from a healthcare professional.

Adolescents and children:

Adolescents (12-17 years) should follow the schedule of treatment for abrupt cessation of smoking as given above. Where adolescents are unwilling or unable to quit smoking abruptly, advice from a healthcare professional should be sought.

Safety and effectiveness in children who smoke has not been evaluated. NiQuitin Lozenges are not recommended for use in children under 12 years of age.

4.3 Contraindications

NiQuitin Lozenges are contraindicated in:

- those with hypersensitivity to nicotine or any of the excipients;
- children under the age of 12 years and 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.

Patients hospitalised for MI, severe dysrhythmia or CVA who are considered to be haemodynamically unstable should be encouraged to stop smoking with non-pharmacological interventions. 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. Once patients are discharged from hospital they can use NRT as

normal. 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:* Potential risks and benefits of nicotine should be carefully evaluated before use 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.

Sodium content: Each NiQuitin Lozenge contains 15 mg of sodium. People on a low sodium diet should take this into account.

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

4.6 Fertility, Pregnancy and lactation

Pregnancy

Stopping smoking is the single most effective intervention for improving the health of both the pregnant smoker and her baby, and the earlier abstinence is achieved the better. However, if the mother cannot (or is considered unlikely to) quit without pharmacological support, NRT may be used as the risk to the foetus is lower than that expected with smoking tobacco. Stopping completely is by far the best option but NRT may be used in pregnancy as a safer alternative to smoking. Because of the potential for nicotine-free periods, intermittent dose forms are preferable, 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.

Lactation

The relatively small amounts of nicotine found in breast milk during NRT use are less hazardous to the infant than second-hand smoke. Intermittent dose forms would minimize the amount of nicotine in breast milk and permit feeding when levels were at their lowest.

4.7 Effects on ability to drive and use machines

Not applicable.

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 Lozenges have not been found to cause any serious adverse effects. 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, sleep disturbance, increased coughing or a cold.

Related adverse events with excess in active compared to placebo group in a controlled study.

Immune system disorders

Very rare <1/10000: anaphylactic reactions

Platelet bleeding and clotting disorders

Uncommon >1/1000; <1/100: gingival bleeding; nosebleed

Psychiatric disorders

Common >1/100; <1/10: insomnia; anxiety; irritability; increased appetite

Uncommon >1/1000; <1/100: anger; aggravated anxiety; abnormal dreaming; abnormal hunger; mood swings; wakefulness

Nervous system disorders

Common >1/100; <1/10: headache

Uncommon >1/1000; <1/100: lightheaded feeling; localised numbness

Not known: seizures

Heart rate and rhythm disorders

Uncommon >1/1000; <1/100: aggravated palpitations; palpitations; tachycardia

Vascular (extracardiac) disorders

Uncommon >1/1000; <1/100: vascular disorder; flushing; skin flushed

Respiratory system disorders

Common >1/100; <1/10: pharyngitis

Uncommon >1/1000; <1/100: laryngismus; aggravated asthma; lower respiratory tract infection; coughing; nasal irritation; throat irritation; nasal congestion

Gastrointestinal system disorders

Very common >1/10: nausea

Common >1/100; <1/10: vomiting; dyspepsia, heartburn, indigestion; hiccup; mouth irritation, mouth ulceration; tongue ulceration; diarrhoea; belching; flatulence

Uncommon >1/1000; <1/100: peptic ucler; dysphagia; aggravated dyspepsia; gastroesophageal reflux; hiatus hernia; oesophagitis; eructation; buccal mucosa ulceration; borborygmus; dry lips; dry throat; tongue disorder; tooth ache

Special senses other, disorders

Uncommon >1/1000; <1/100: parageusia, metallic taste; taste perversion

Skin and appendages disorders

Uncommon >1/1000; <1/100: erythema; itching; rash; skin reaction localised; increased sweating

Musculoskeletal system disorders

Uncommon >1/1000; <1/100: jaw pain

Urinary system disorders

Uncommon >1/1000; <1/100: nocturia

Body as a whole - general disorders

Uncommon >1/1000; <1/100: overdose effect; pain; leg pain; oedema legs

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 gastrointestinal absorption of nicotine.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: N07B A01

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

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 4.4 ng/ml. When dosed every 1.5 hours, the steady state peak and trough concentrations are 12.7 and 9.4 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.

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.

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.

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. Effects on fertility have not been established.

Comparison of the systemic exposure necessary to elicit these adverse responses from preclinical test systems with that associated with the recommended use of NiQuitin Lozenges indicate that the potential risk is low and outweighed by the demonstrable benefit of nicotine therapy in smoking cessation. However, NiQuitin Lozenges should only be used by pregnant women on medical advice if other forms of treatment have failed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol

Sodium alginate

Xanthan gum

Potassium bicarbonate

Calcium polycarbophil

Sodium carbonate anhydrous

Aspartame

Magnesium stearate

Menthol mint flavour

6.2 Incompatibilities

None known.

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, 72, 96, 108 and 144.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

None.

7 MARKETING AUTHORISATION HOLDER

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