SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

NiQuitin 7 mg transdermal patches

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 7 cm^2 transdermal patch contains 36 mg nicotine, equivalent to 5.1 mg/cm^2 of nicotine and delivering 7 mg over 24 hours.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Transdermal patch.

Each patch is rectangular and is comprised of an outer matt pinkish tan-coloured layer, a middle silver layer and an outer clear layer which is removed prior to use.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

If possible, when stopping smoking, NiQuitin patches should be used in conjunction with a behavioural support programme.

4.2 Posology and method of administration

NiQuitin patches should be applied once a day, at the same time each day and preferably soon after waking, to a different non-hairy, clean, dry skin site and worn continuously for 24 hours. The NiQuitin patch should be applied promptly on removal from its protective sachet. It should be pressed firmly on the skin with the palm of hand for 10 seconds. Areas where the skin creases should be avoided.

Avoid applying to any skin which is broken, red or irritated. After 24 hours the used patch should be removed and a new patch applied to a fresh skin site. The patch should not be left on for longer than 24 hours. Skin sites should not be reused for at least seven days. Only one patch should be worn at a time.

The patch should be kept sealed in its protective sachet until ready to use. The user should wash hands with water after handling the patch, and avoid contact with eyes and nose.

Patches may be removed before going to bed if desired. However use for 24 hours is recommended to optimise the effect against morning cravings.

Water will not harm the nicotine transdermal patch, if it has been applied properly. The user can bathe, swim or shower for short periods while wearing the nicotine transdermal patch.
Concurrent behavioural support is recommended, as such programmes have been shown to be beneficial for smoking cessation.

Adults 18 years and over

Abrupt cessation of

smoking:

During a quit attempt every effort should be made to stop smoking with NiQuitin patches.

NiQuitin therapy should usually begin with NiQuitin 21 mg and be reduced according to the following dosing schedule:-

Dose	**Duration**
Step 1 NiQuitin 21 mg	First 6 weeks
Step 2 NiQuitin 14 mg	Next 2 weeks
Step 3 NiQuitin 7 mg	Last 2 weeks

Light smokers (e.g. those who smoke less than 10 cigarettes per day) are recommended to start at Step 2 (14 mg) for 6 weeks and decrease the dose to NiQuitin 7 mg for the final 2 weeks.

Patients on NiQuitin 21 mg who experience excessive side-effects (please refer to precautions), which do not resolve within a few days, should change to NiQuitin 14mg. This strength should then be continued for the remainder of the 6 week course before stepping down to NiQuitin 7mg for two weeks. If the symptoms persist the patient should be advised to seek the advice of a healthcare professional.

For optimum results, the 10 week treatment course (8 weeks for light smokers or patients who have reduced strength as above), should be completed in full. Treatment with NiQuitin patch may be continued beyond 10 weeks if needed to stay cigarette free, however, those who have quit smoking but are having difficulty discontinuing using the patches recommended to seek additional help and advice from a healthcare professional.

Further courses may be used at a later time, for NiQuitin patch users who continue or resume smoking.

Gradual Cessation:

For smokers who are unwilling or unable to quit abruptly.

The 21 mg patch can be used daily for 2-4 weeks while the user continues to smoke as needed. At the end of the 2-4 weeks the user should quit completely and continue using Step 1 21 mg patch for 6 weeks daily without smoking. Thereafter following the Step 2 and 3 directions for abrupt cessation above. Should the patient feel able to quit completely before their designated quit date they can do so.

Reduction in smoking:

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

A patch can be used while the user continues to smoke as needed. The user should 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.

If users are still feeling the need to use the patches 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

Apply a patch to control troublesome withdrawal symptoms including craving during the period when smoking is being avoided. Users should be encouraged to stop smoking completely as soon as possible.

If users are still feeling the need to use the patches 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 to 17 years) should follow the schedule of treatment for abrupt cessation of smoking as given above. Where adolescents are not ready or not able to stop smoking abruptly, advice from a healthcare professional should be sought.

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

4.3 Contraindications

NiQuitin is contraindicated in patients with hypersensitivity to the system, the active substance, or any of the excipients.
NiQuitin patches should not be used by non-smokers, occasional smokers or children under 12 years.

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 patches 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 nicotine patch dose should be reduced or discontinued.

Nicotine replacement therapy may exacerbate symptoms in persons suffering from active oesophagitis, oral and pharyngeal inflammation, gastritis, gastric ulcer or peptic ulcer.

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.

*Atopic or eczematous dermatitis (*due to localised patch sensitivity): In the case of severe or persistent local reactions at the site of application (e.g. severe erythema, pruritus or oedema) or a generalised skin reaction (e.g. urticaria, hives or generalised skin rashes), users should be instructed to discontinue use of NiQuitin and contact their physician.

Contact sensitisation: Patients with contact sensitisation should be cautioned that a serious reaction could occur from exposure to other nicotine-containing products or smoking.

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.

- *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.

- *Cardiovascular disease:* The pre-cessation regimen should not be used in people with known cardiovascular disease without evaluation of the risk/benefit by a healthcare professional.

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. After removal, the patch should be folded in half, adhesive side

innermost, and placed inside the opened sachet, or in a piece of aluminium foil. The used patch should then be disposed of with care.

Patches should be kept out of the sight and reach of 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.

Safety on handling: NiQuitin is potentially a dermal irritant and can cause contact sensitisation. Care should be taken during handling and in particular contact with the eyes and nose avoided. After handling, wash hands with water alone as soap may increase nicotine absorption.

Users who initiate quitting with pre-cessation NRT and experience exaggerated effects as listed in 'overdose' (see section 4.9) should discontinue smoking and if the symptoms persist remove the patch. If symptoms improve after smoking cessation, the user may resume using the patch.

4.5 Interaction with other medicinal products and other forms of interaction

No clinically relevant interactions between nicotine replacement therapy and other drugs has definitely been established, however nicotine may possibly enhance the haemodynamic effects of adenosine.
Healthcare professionals are reminded that 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 as intra-uterine growth retardation, premature birth or stillbirth. 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. Ideally smoking cessation during pregnancy should be achieved without NRT. However, if the mother cannot (or is considered unlikely to) quit without pharmacological support, 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 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. If patches are used, they should be removed at night before going to bed when the foetus would not normally be exposed to nicotine.

Lactation
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 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
Effects of nicotine on male reproductive tissues have been observed in rats (see section 5.3), however the clinical significance is unknown.

4.7 Effects on ability to drive and use machines

NiQuitin Patches 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 may cause adverse reactions similar to those associated with nicotine administered by other means, including smoking. These may be attributable to the pharmacological effects of nicotine, some of which are dose dependent. At recommended doses, NiQuitin patches have not been found to cause any serious adverse effects. Excessive use of NiQuitin patches by those who have not been in the habit of inhaling tobacco smoke could possibly lead to nausea, faintness or headaches.

Subjects quitting smoking by any means could expect to suffer from asthenia, headache, dizziness, sleep disturbance, coughing or influenza-like illness. Certain symptoms which have been reported such as depression, irritability, nervousness, restlessness, mood lability, anxiety, drowsiness, impaired concentration and insomnia may be related to withdrawal symptoms associated with smoking cessation.

Application site reactions are the most frequent adverse reaction associated with NiQuitin. NiQuitin can cause other adverse reactions related to the pharmacological effect of nicotine or withdrawal effects related to smoking.

The following undesirable effects have been reported in clinical trials or spontaneously post-marketing.

Certain symptoms which have been reported such as depression, irritability, nervousness, restlessness, mood lability, anxiety, drowsiness, impaired concentration, insomnia and sleep disturbances may be related to withdrawal symptoms associated with smoking cessation. Subjects quitting smoking by any means could expect to suffer from asthenia, headache, dizziness, coughing or influenza-like illness.

Immune System Disorders
Uncommon>1/1000; <1/100: hypersensitivity NOS*
Very rare <1/10000: anaphylactic reactions

Psychiatric
Very common >1/10: sleep disorders including abnormal dreams and insomnia
Common >1/100; <1/10: nervousness

Nervous system disorders
Very Common >1/10: headache, dizziness
Common >1/100; <1/10: tremor
Not known: seizures

Cardiac disorders
Common >1/100; <1/10: palpitations
Uncommon >1/1000; <1/100: tachycardia NOS

Respiratory, Thoracic and Mediastinal Disorders
Common >1/100; <1/10: dyspnoea, pharyngitis, cough

Gastrointestinal Disorders
Very Common >1/10: nausea, vomiting
Common >1/100; <1/10: dyspepsia, abdominal pain upper, diarrhea NOS, dry mouth, constipation

Skin and Subcutaneous Tissue Disorders
Common >1/100; <1/10: sweating increased
Very rare > 1/100000; <1/10000: dermatitis allergic*, dermatitis contact*, photosensitivity

Musculoskeletal and Connective Tissue Disorders
Common >1/100; <1/10: arthralgia, myalgia

General Disorders and Administration Site Conditions
Very Common >1/10: application site reactions NOS*
Common >1/100; <1/10: chest pain, pain in limb, pain NOS, asthenia, fatigue
Uncommon >1/1000; <1/100 malaise, influenza-like illness

* see below

Application site reactions, including transient rash, itching, burning, tingling, numbness, swelling, pain and urticaria are the most frequent undesirable effects of NiQuitin patch. The majority of these topical reactions are minor and resolve quickly following removal of the patch. Pain or sensation of heaviness in the limb or area around which the patch is applied (e.g. chest) may be reported.

Hypersensitivity reactions, including contact dermatitis and allergic dermatitis have also been reported. In the case of severe or persistent local reactions at the application

site (e.g. severe erythema, pruritus or oedema) or a generalized skin reaction (e.g. urticaria, hives or generalised skin rashes) users should be instructed to discontinue use of NiQuitin and contact their physician.

If there is a clinically significant increase in cardiovascular or other effects attributable to nicotine, the NiQuitin dose should be reduced or discontinued.

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 Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 a nicotine patch 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

Overdose from Topical Exposure

The nicotine patch(es) should be removed immediately in the event of an overdose or if the patient shows signs of overdosage. The user should seek medical attention immediately. The skin surface may be flushed with water and dried. No soap should be used since it may increase nicotine absorption. Nicotine will continue to be delivered into the bloodstream for several hours after removal of the system because of a depot of nicotine in the skin.

Overdose from Ingestion

All nicotine intake should stop immediately. The patient should seek medical attention immediately and 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

Pharmacotherapeutic classification: N07B A01

(Anti-smoking agents: N07BA, Nicotine 01)

Nicotine, the chief alkaloid in tobacco products and a naturally occurring autonomic drug, is an agonist at nicotine receptors in the peripheral and central nervous system and has pronounced CNS and cardiovascular effects. Withdrawal from nicotine in addicted individuals is characterised by craving, nervousness, restlessness, irritability, mood lability, anxiety, drowsiness, sleep disturbances, impaired concentration, increased appetite, minor somatic complaints (headache, myalgia, constipation, fatigue) and weight gain. Withdrawal symptoms, such as cigarette craving, may be controlled in some individuals by steady-state plasma levels lower than those for smoking.

In clinically controlled trials, NiQuitin was shown to alleviate nicotine withdrawal symptoms as well as craving. NiQuitin reduced the severity of cravings by at least 35% at all times of day during the first two weeks of abstinence, compared to placebo ($p<0.05$).

5.2 Pharmacokinetic properties

Absorption

Following transdermal application, the skin rapidly absorbs nicotine released initially from the patch adhesive. The plasma concentrations of nicotine reach a plateau within 2-4 hours after initial application of NiQuitin with relatively constant plasma concentrations persisting for 24 hours or until the patch is removed. Approximately 68% of the nicotine released from the patch enters systemic circulation and the remainder of the released nicotine is lost via vaporisation from the edge of the patch.

With continuous daily application of NiQuitin (worn for 24 hours), dose-dependent steady state plasma nicotine concentrations are achieved following the second NiQuitin application and are maintained throughout the day. These steady state maximum concentrations are approximately 30% higher than those following a single application of NiQuitin.

Plasma concentrations of nicotine are proportional to dose for the three dosage forms of NiQuitin. The mean plasma steady state concentrations of nicotine are approximately 17 ng/ml for the 21 mg/day patch, 12 ng/ml for the 14 mg /day patch and 6 ng/ml for the 7 mg/day patch. For comparison, half-hourly smoking of cigarettes produces average plasma concentrations of approximately 44 ng/ml.

The pronounced early peak in nicotine blood levels seen with inhalation of cigarette smoke is not observed with NiQuitin.

Distribution

Following removal of NiQuitin, plasma nicotine concentrations decline with an apparent mean half-life of 3 hours, compared with 2 hours for IV administration due to continued absorption of nicotine from the skin depot. If NiQuitin is removed most non-smoking patients will have non-detectable nicotine concentrations in 10 to 12 hours.

A dose of radiolabelled nicotine given intravenously showed a distribution of radioactivity corresponding to the blood supply with no organ selectively taking up nicotine. The volume of distribution of nicotine is approximately 2.5 l/kg.

Metabolism

The major elimination organ is the liver and average plasma clearance is about 1.2 l/min; the kidney and the lung also metabolise nicotine. More than 20 metabolites of nicotine have been identified, all of which are believed to be pharmacologically inactive. The principal metabolites are cotinine and trans-3-hydroxycotinine. Steady state plasma cotinine concentrations exceed nicotine by 10-fold. The half-life of nicotine ranges from 1 to 2 hours and cotinine's between 15 and 20 hours.

Excretion

Both nicotine and its metabolites are excreted through the kidneys and about 10% of nicotine is excreted unchanged in the urine. As much as 30% may be excreted in the urine with maximum flow rates and extreme urine acidification ($pH \leq 5$).

There were no differences in nicotine kinetics between men and women using NiQuitin. Obese men using NiQuitin had significantly lower AUC and Cmax values compared with normal weight men. Linear regression of AUC vs total body weight showed the expected inverse relationship (AUC decreases as weight increases).

Nicotine kinetics were similar for all sites of application on the upper body and upper outer arm.

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.

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.

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

Comparison of the systemic exposure necessary to elicit these adverse responses from preclinical test systems with that associated with the recommended use of NiQuitin indicate that the potential risk is low and outweighed by the demonstrable benefit of nicotine therapy in smoking cessation. However, NiQuitin 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

Drug Reservoir:	Ethylene Vinyl Acetate Copolymer
Occlusive Backing:	Polyethylene/Aluminium/Polyethylene Terephthalate/ Ethylene vinyl acetate
Rate Controlling Membrane:	Polyethylene Film
Contact Adhesive and Protective Layer:	Polyisobutylene Adhesive Laminate
Printing Ink:	FGN-7214 NT20 Brown 465 (Ink)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

7 or 14 patches in a carton. Each patch is contained in a laminate sachet.

6.6 Special precautions for disposal

Nicotine residues in the used patches are a hazard to children and pets. Used patches should be folded, sticky sides together, put back in the empty sachet or in a piece of aluminum foil and disposed of in accordance with local requirements.

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

7 MARKETING AUTHORISATION HOLDER

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