SUMMARY OF THE PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

NiQuitin 7 mg/24 hours transdermal patch
NiQuitin 14mg/24 hours transdermal patch
NiQuitin 21mg/24 hours transdermal patch

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each (7 cm^2) patch of 7 mg/24 hours contain 36 mg nicotine
Each (15cm^2) patch of 14 mg/24 hours contain 78 mg nicotine
Each (21 cm^2) patch of 21 mg/24 hours contain 114 mg nicotine

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Transdermal patch.

21 mg/24 hours is marked NCQ 21
14 mg/24 hours is marked NCQ 14
7 mg/24 hours is marked NCQ 7

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

NiQuitin is indicated for the relief of nicotine withdrawal symptoms associated with smoking cessation. If possible, when stopping smoking, NiQuitin should be used in conjunction with a behavioural support programme.

4.2 Posology and method of administration

The patches should be used as directed below. Prior to initiation of therapy users should be committed to stopping smoking. During a quit attempt, any smoking is very likely to lead to relapse. Therefore users must not smoke during a cessation attempt. No other form of nicotine should be taken at the same time. Concurrent behavioural support is recommended; as such programmes have been shown to be beneficial for smoking cessation.

Posology

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*

Smokers with low nicotine dependence (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.

NiQuitin 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 7 mg 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 patients who have reduced strength as above), should be completed in full. It should not extend beyond 10 consecutive weeks.
However, further courses may be used at a later time, for NiQuitin users who continue or resume smoking.

Paediatric population

Safety and efficacy in children and adolescents who smoke have not been evaluated. NiQuitin is not recommended for use in children. NiQuitin should only be used in adolescents (aged 12 – 17 years) with advice from a doctor.

Method of administration

A new NiQuitin patch should be applied once a day, at the same time each day and preferably soon after awakening, 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.

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

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

NiQuitin patches should not be used by non-smokers, occasional smokers or children.

NiQuitin should not be used in patients with recent myocardial infarction, unstable or worsening angina pectoris, Prinzmetal’s angina, severe cardiac arrythmias, or recent cerebrovascular accident.

4.4 Special warnings and precautions for use

Paediatric population

The amounts of nicotine that are tolerated by adult smokers can produce symptoms of poisoning and could prove fatal if NiQuitin is applied by children, or ingested by children. Even used NiQuitin patches contain enough residual nicotine to be harmful to children.

Patients should therefore be warned to keep patches out of the reach of children and instructed to dispose of used patches carefully in a place away from children.

Safety on Handling

NiQuitin is potentially a dermal irritant and can cause contact sensitization. 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.

Precautions

Patients must stop smoking and using any other form of nicotine completely when starting and throughout NiQuitin therapy. Patients should be warned that if they continue to smoke or use any additional source of nicotine while using NiQuitin there is a potential to experience adverse effects due to peak nicotine levels higher than those experienced from smoking or using other nicotine products alone. If there is a clinically significant increase in cardiovascular or other effects attributable to nicotine, the NiQuitin dose should be reduced or discontinued. Concomitant medications may need dosage adjustment (see Drug Interactions). The maximum duration of a treatment course is 10 weeks. Patients should not continue beyond this treatment period because the chronic consumption of nicotine can be toxic and addicting. Tachycardia occurring in association with the use of NiQuitin was reported occasionally.

NiQuitin should be used only with medical advice in patients with:

- cardiovascular disease (e.g. stable angina pectoris, heart failure, cerebrovascular disease, vasospastic diseases, severe peripheral vascular disease),
- uncontrolled hypertension, since nicotine may be a risk factor for the development of malignant hypertension,
- atopic or eczematous dermatitis (due to localised patch sensitivity)
- severe renal or hepatic impairment or active peptic ulcers,
- hyperthyroidism, pheochromocytoma or insulin-dependent diabetes.
- 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.

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 physicians.

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

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

4.5 Interaction with other medicinal products and other forms of interaction

Smoking cessation, with or without nicotine substitutes, may alter the response to concomitant medication in ex-smokers.
The following drugs may require adjustment in dose at cessation of smoking.

May require a **decrease** in dose at cessation of smoking	Possible mechanism of action

Caffeine, theophylline, imipramine, pentazocine, phenacetin, phenylbutazone, tacrine, clomipramine. Insulin Adrenergic blockers eg prazosin, propranolol.	Reduced induction of CYP1A2 Increase in sub-cutaneous insulin absorption Decreases circulating catecholamines
May require an **increase** in dose at cessation of smoking	Possible mechanism of action
Adrenergic agonists e.g. isoprenaline, salbutamol	Decreases in circulating catecholamines

4.6 Fertility, pregnancy and lactation

Fertility

Effects on human fertility have not been established. Animal studies on fertility are considered to have limited relevance to the clinical use of transdermal nicotine, since the overall dose and routes of exposure cannot be directly correlated to the controlled use of a transdermal nicotine replacement therapy [refer 5.3 Preclinical Safety Data]

Pregnancy

Nicotine passes on to the foetus and affects the breathing pattern and circulation of the foetus. The effect on the circulation of the foetus is dose-dependent.

Pregnant smokers should therefore always be recommended to stop smoking without nicotine replacement therapy. The risk of continuous smoking may pose a greater risk for the foetus than the use of nicotine replacement therapy and medical assessment of the risk/benefit ratio of the use of NiQuitin should be made. NiQuitin should not be used by others than pregnant women with high nicotine dependence on doctor's advice.

Breastfeeding

Nicotine passes freely into breast milk in quantities that may affect the child even with therapeutic doses. NiQuitin should therefore be avoided during breastfeeding. Should smoking cessation not be achieved, use of NiQuitin by breastfeeding mothers should only be initiated after advice from a healthcare professional.

4.7 Effects on ability to drive and use machines

There are no known effects of NiQuitin on the ability to drive and use machines.

4.8 Undesirable effects

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 ability, 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*
Not known (cannot be estimated from the available data): anaphylactic reactions

Psychiatric disorders
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

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, diarrhoea 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*, photosensitvity

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 generalised skin reaction (e.g. urticaria 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.

<u>Reporting of suspected adverse reactions</u>

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 the national reporting system listed in Appendix V

4.9 Overdose

The effects of applying several NiQuitin patches simultaneously or swallowing NiQuitin patches are unknown.
Signs and symptoms of an overdose from a NiQuitin patch would be expected to be the same as those of acute nicotine poisoning, including pallor, cold sweat, nausea, salivation, vomiting, abdominal pain, diarrhoea, headache, dizziness, disturbed hearing and vision, tremor, mental confusion and weakness. Prostration, hypotension, respiratory failure and convulsions may ensue with large overdoses. Lethal doses produce convulsions quickly and death follows as a result of peripheral and central respiratory paralysis or, less frequently, cardiac failure.

Overdose from topical exposure

The NiQuitin patch should be removed immediately if the patient shows signs of overdosage and the patient should seek immediate medical care. 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 patch because of a depot of nicotine in the skin.

Overdose from ingestion

Activated charcoal should be administered as long as the patch remains in the gastrointestinal tract since it will continue to release nicotine for many hours.

Management of nicotine poisoning

Other supportive measures include diazepam or barbiturates for seizures, atropine for excessive bronchial secretions or diarrhoea, respiratory support for respiratory failure and vigorous fluid support for hypotension and cardiovascular collapse.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in nicotine dependence
ATC-code: N07BA01

Nicotine, the chief alkaloid in tobacco products, 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 liability, 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 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. The bioavailability of the nicotine released from the patch is approx. 70% and the remainder of the released nicotine evaporates from the edge of the patch.
With daily application of NiQuitin (worn for 24 hours), steady state plasma nicotine concentrations are achieved following the second NiQuitin application and are maintained throughout the day. 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 strengths 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 high nicotine plasma concentrations seen initially from smoking are 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.
Less than 5% of nicotine is bound to plasma proteins, and a dose of radio labelled 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. Nicotine can pass the blood-brain barrier.

Metabolism

Nicotine is mainly metabolised in the liver, and average plasma clearance is about 1.2 l/min; nicotine is also metabolised by the kidney and the lung. 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 elimination half-life of nicotine ranges from 1 to 2 hours and cotinine's between 15 and 20 hours.

Elimination

Both nicotine and its metabolites are excreted through the kidneys. The amount of unmetabolised nicotine which is excreted is pH-dependent. At maximum flow and extreme urine acidification (pH<5) the amount can be as much as 30%, but normally the amount is about 10%.

Special patient groups

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. Nicotine kinetics was 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 documented. Nicotine was not mutagenic or carcinogenic in conventional assays. In studies in pregnant animals, at exposure levels resulting in maternal toxicity (in excess of those that will be obtained with the recommended use of NiQuitin), a mild foetal toxicity was seen. Other effects included pre- and postnatal growth retardation and delays and changes in postnatal CNS development. Effects on fertility have not been established.

Nicotine has been reported to induce changes to the ovary and uterus of female rats and mice following repeated oral or intraperitoneal administration of doses exceeding those that result from the recommended use of NiQuitin. Repeated intraperitoneal or oral administration of nicotine to male rats at doses exceeding those resulting from the recommended use of NiQuitin was reported to cause a decrease in testis weight, changes in the epididymis and vas deferens, and a reversible decrease in Sertoli cell numbers with impairment of spermatogenesis.

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:	PMS 465 Brown Ink

6.2 Incompatibilities

Not relevant.

6.3 Shelf-life

21 mg/24 hours:	3 years
14 mg/24 hours:	2 years
7 mg/24 hours:	2 years

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and content of container

21 mg/24 hours	7 or 14 patches.
14 mg/24 hours	7 or 14 patches.
7 mg/24 hours	7 or 14 patches.

Each patch is rectangular and is comprised of an outer matt light brown coloured layer, a middle silver layer and an outer clear layer. Each patch is contained in a laminate sachet.

6.6 Special precautions for disposal

Not applicable.

7 MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Consumer Healthcare A/S
Nykær 68
2605 Brøndby
Denmark

8 MARKETING AUTHORISATION NUMBER(S)

21 mg/24 hours:	12114
14 mg/24 hours:	12113
7 mg/24 hours:	12112

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

1994-04-22/2009-04-22

10 DATE OF REVISION OF THE TEXT

2017-09-22