Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

NiQuitin CLEAR 7 mg/24 hrs transdermal patch

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

NiQuitin CLEAR is a transdermal delivery system for transdermal use available in systems of 7 cm^2 containing36 mg nicotine,equivalent to 5.1 mg/cm^2 of nicotine and delivering 7 mg over 24 hours.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Transdermal patch.

Each patch is rectangular and is comprised of clear backing and a protective liner which is removed prior to use.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

NiQuitin CLEAR is indicated for the relief of nicotine withdrawal symptoms including cravings as an aid to smoking cessation. If possible, when stopping smoking, NiQuitin CLEAR should be used in conjunction with a behavioural support programme.
NiQuitin CLEAR is indicated in adults and adolescents aged 12 years and over.
NiQuitin CLEAR can be used in combination with oral nicotine forms (gums or lozenges) in smokers who have relapsed after nicotine replacement therapy (NRT), or when monotherapy with one NRT is not sufficient to control cravings, or as first line treatment in smokers with a high level of dependence, such as those smoking 10 or more cigarettes in a day. (See section 4.2).
Adolescents should not quit with a Combination NRT regime.

4.2 Posology and method of administration

Posology

Adults (18 years and over)

The patches should be used as directed below. Prior to initiation of therapy users should be committed to stopping smoking. During a quit attempt, every effort should be made to stop smoking during treatment with NiQuitin CLEAR. Concurrent behavioural support is recommended, as such programmes have been shown to be beneficial for smoking cessation.NiQuitin CLEAR patches should be applied once a day, at the same time each day and preferably soon after waking and worn continuously for 24 hours.
In some instances (e.g. in heavy smokers, or those who have relapsed after NRT before, or when one NRT is not enough to control cravings - see section 4.1), it may also be beneficial to utilise more than one form of NiQuitin concurrently. For example, smokers who have difficulty controlling cravings when using a patch alone may use a gum, a lozenge or a mini lozenge to support sudden cravings.
NiQuitin Clear patches may be used alone or in combination with any NiQuitin 1.5mg/2mg/4mg oral lozenge, mini lozenge or gum (refer to detailed combination therapy posology below).
NiQuitin CLEAR therapy should usually begin with NiQuitin CLEAR 21 mg/24 hrs and be reduced according to the following dosing schedule:
Table 1: NiQuitin Clear Dosing Schedule

Dose		Duration
Step 1	NIQuitin CLEAR 21mg/24 hrs	First 6 weeks
Step 2	NIQuitin CLEAR 14mg/24 hrs	Next 2 weeks
Step 3	NIQuitin CLEAR 7mg/24 hrs	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 CLEAR 7 mg/24 hrs for the final 2 weeks.
Patients on NiQuitin CLEAR 21 mg/24 hrs who experience excessive side effects, which do not resolve within a few days, should change to NiQuitin CLEAR 14 mg/24 hrs. This strength should then be continued for the remainder of the 6 week course before stepping down to NiQuitin CLEAR 7 mg/24 hrs 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 CLEAR patch may be continued beyond 10 weeks if needed to stay cigarette free, however, those who use the patches beyond 9 months are recommended to seek additional help and advice from a healthcare professional.
Further courses may be used at a later time, for NiQuitin CLEAR users who continue or resume smoking.
Combination therapy: Treatment with NiQuitin Clear Patch in combination with NiQuitin 1.5mg/2mg/4mg lozenge, mini lozenge or gum.
Smokers can combine the transdermal patches and oral forms of nicotine (gum, lozenges, etc.). The combination of transdermal patches and oral forms of nicotine gives better effectiveness than using transdermal patches alone.
The initial treatment should begin with the determination of the dose of the patch - according to the same rules as the monotherapy (see above) - in combination with a dose of oral nicotine. The daily intake of oral preparations, when combined with patches, is recommended to be around 5 to 6 pieces. When used in combination the maximum daily dose for 4mg oral forms is 10 pieces and for 1.5mg/2mg oral forms remains 15 pieces.

Table 2: Recommended dosage for combination therapy-Adults who smoke more than 10 cigarettes a day

Period	**Patches**	**NiQuitin 2mg/4mg gum/lozenge or 1.5mg/4mg mini lozenge**
Step 1: 6 weeks	NiQuitin 21 mg / 24 hours	5 to 6 pieces per day*
Step 2: 2 weeks	NiQuitin 14 mg / 24 hours	Continue to use lozenge/mini lozenge/gum, when necessary*
Step 3: 2 weeks	NiQuitin 7 mg / 24 hours	
After 10 weeks	Stop using NiQuitin patches	Reduce the number of lozenge/mini lozenge/gum gradually. When daily use is reduced to 1-2 pieces, treatment should be stopped.

*Smokers who smoke more than 20 cigarettes should use 4 mg oral dose for the first 6 weeks. Thereafter reducing to a lower strength oral dose. The maximum daily dose for 4mg oral forms is 10 pieces and for 1.5mg/2mg oral forms is 15 pieces.

Table 3: Recommended dosage for combination therapy-Adults who smoke less than 10 cigarettes a day

Period	**Patches**	**NiQuitin 2mg gum/lozenge or 1.5 mg mini lozenge**
Step 2: 6 weeks	NiQuitin 14 mg / 24 hours	5 to 6 pieces per day†
Step 3: 2 weeks	NiQuitin 7 mg / 24 hours	Continue to use lozenge/mini lozenge/gum, when necessary†
After 8 weeks	Stop using NiQuitin patches	Reduce the number of lozenge/mini lozenge/gum gradually. When daily use is reduced to 1-2 pieces, treatment should be stopped.

† The maximum daily dose for 1.5mg/2mg oral forms is 15 pieces.
The treatment duration depends on the needs of each smoker. In general, the use of oral NiQuitin preparations is 2 - 3 months, then use may be reduced gradually. When daily use is reduced to 1-2 doses, use should be stopped.

Paediatric population

Adolescents (12 to 17 years) should follow the schedule of treatment for adults presented above in Table 1 for steps 1, 2 and 3, but as data are limited, duration of NRT in this age group is restricted to 12 weeks. If longer treatment is required advice from a healthcare professional should be sought. Due to an absence of data adolescents should not quit with a Combination NRT regimen.
NiQuitin CLEAR is contraindicated in children under 12 years of age.

Method of administration

A new NiQuitin CLEAR patch should be applied to a different non-hairy, clean, dry skin site. The NiQuitin CLEAR patch should be applied promptly on removal from its protective sachet. The patch should be kept sealed in its protective sachet until ready to use. 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 optimise the effect against morning cravings.
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.

4.3 Contraindications

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

NiQuitin CLEAR patches should not be used by:
- children under 12 years
- occasional smokers
- 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 CLEAR 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 closely monitor their blood glucose levels 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 CLEAR and contact their physician. This may be more likely if there is a history of dermatitis.
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*: 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. After removal the patches should be folded in half with the 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.
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 CLEAR is potentially a dermal irritant and can cause contact sensitisation.
Patches should be kept out of the sight and reach of children.

Special warnings and precautions for use for combined treatment with NiQuitin transdermal patches and oral NiQuiitn preparations are the same as for each treatment alone (see SPC for respective oral preparation used in combination).
The combination NRT regimen should not be used in people with known cardiovascular disease without evaluation of the risk/benefit by a healthcare professional.

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 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. If patches are used they should be removed before going to bed.
Due to an absence of specific studies, combination therapy with patches and oral forms is not recommended during pregnancy unless the healthcare professional considers it necessary to ensure abstinence.

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, 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),

4.7 Effects on ability to drive and use machines

NiQuitin CLEAR transdermal patch has 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

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).

Application site reactions are the most frequent adverse events associated with NiQuitin CLEAR patches. Other adverse events may occur and may be related to the pharmacological effects of nicotine or withdrawal effects related to stopping smoking (see Pharmacodynamic Effects).

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.

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

System Organ Class and Frequency	**Adverse Reaction/Event**
Immune System Disorders	
Uncommon	hypersensitivity*
Very rare	anaphylactic reactions
Psychiatric	
Very common	sleep disorders including abnormal dreams and insomnia
Common	nervousness
Nervous system disorders	
Very Common	headache, dizziness
Common	tremor
Cardiac Disorders	
Common	palpitations
Uncommon	tachycardia
Respiratory, Thoracic and Mediastinal Disorders	
Common	dyspnoea, pharyngitis, cough
Gastrointestinal Disorders	
Very Common	nausea, vomiting
Common	dyspepsia, upper abdominal pain, diarrhoea, dry mouth, constipation
Skin and Subcutaneous Tissue Disorders	
Common	increased sweating
Very rare	allergic dermatitis *, contact dermatitis *, photosensitivity
Musculoskeletal and Connective Tissue Disorders	
Common	arthralgia, myalgia
General Disorders and Administration Site Conditions	
Very common	application site reactions*
Common	chest pain*, pain in limb*, pain, asthenia, fatigue/malaise
Uncommon	influenza-like illness

* The majority of 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.

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

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 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 group: Drugs used in nicotine dependence

ATC code: N07BA01

Mechanism of action
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.

Clinical efficacy and safety
In clinically controlled trials nicotine withdrawal symptoms were alleviated as well as craving. The severity of craving was reduced 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 CLEAR 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 CLEAR (worn for 24 hours), dose-dependent steady state plasma nicotine concentrations are achieved following the second NiQuitin CLEAR application and are maintained throughout the day. These steady state maximum concentrations are approximately 30% higher than those following a single application of NiQuitin CLEAR.

Plasma concentrations of nicotine are proportional to dose for the three dosage forms of NiQuitin CLEAR. 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 CLEAR.

Distribution

Following removal of Ni Quitin CLEAR, 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 CLEAR is removed most non-smoking patients will have non-detectable nicotine concentrations in 10 to 12 hours.

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.

Biotransformation

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.

Elimination

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 ≤5).

There were no differences in nicotine kinetics between men and women using nicotine patches. Obese men using nicotine patch had significantly lower AUC and C_{max} 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. Effects were only noted following exposure to nicotine at levels in excess of those which will result from recommended use of NiQuitin CLEAR. Studies in male rats have shown that nicotine can decrease testis weight, cause a reversible

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Drug Reservoir: Ethylene Vinyl Acetate Copolymer
Occlusive Backing: Polyethylene Terephthalate/Ethylene vinyl acetate
Rate Controlling Memebrane: Polyethylene Film

Contact Adhesive and Protective Layer: Polyisobutylene Adhesive Laminate
Printing Ink: 3015Z-009L White Ink

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 30ºC

6.5 Nature and contents of container

Each patch is contained in a laminate sachet.

7, 14, 21, 28 or 42 patches in a carton. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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 aluminium 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

Chefaro Ireland DAC
The Sharp Building
Hogan Place
Dublin 2
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1186/018/004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27 September 2002
Date of last renewal: 02 April 2006

10 DATE OF REVISION OF THE TEXT

October 2020