Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Nicorette Invisi Extra Strength 25mg/16 hours Transdermal Patch

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Nicotine, 25mg released over 16 hours use. Each patch is 22.5cm^2, containing 1.75mg nicotine / cm^2.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Transdermal Patch
Beige semi-transparent patch consisting of pre-coated backing layer, nicotine source layer, a skin contact adhesive layer on a pre-coated, aluminized and siliconised release layer with "nicorette" printed on the top face of the patch. The patch is approximately 4 x 5cm (with rounded corners).

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of tobacco dependence by relieving nicotine craving and withdrawal symptoms, thereby facilitating smoking cessation in smokers motivated to quit.

4.2 Posology and method of administration

Adults and the Elderly
Experience with the treatment of nicotine dependence shows that success rates are improved if patients also receive support therapy and counseling. Nicorette Invisi Patch should not be used concurrently with any other nicotine products and patients must stop smoking completely when starting treatment.

The patch should be applied to an intact area of the skin upon waking up in the morning and removed at bedtime. Patch treatment mimics the fluctuations of nicotine over the day in smokers, with no nicotine administration during sleep. Daytime nicotine patch treatment does not give the nicotine induced sleep disturbances seen with nicotine administration during sleep.

Heavy smokers are recommended to start at Step 1 with the 25 mg/ 16 hours patch and use one patch daily for 8 weeks.

Gradual weaning from the patch should then be initiated. One 15 mg/16 hours patch should be used daily for 2 weeks followed by one 10 mg/16 hours patch daily for 2 weeks.
Light smokers are recommended to start at Step 2 (15 mg) for 8 weeks and decrease the dose to Step 3 (10 mg) for the final 4 weeks.Table 1 Heavy Smokers Light Smokers

Dose regimen		Duration	Dose regimen		Duration
Step 1	Nicorette Invisi Patch 25 mg	First 8 weeks			
Step 2	Nicorette Invisi Patch15 mg	Next 2 weeks	Step 2	Nicorette Patch 15 mg	First 8 weeks
Step 3	Nicorette Invisi Patch10 mg	Last 2 weeks	Step3	Nicorette Patch 10 mg	Last 4 weeks

Children and Adolescents
Nicorette Invisi Patch should not be administered to persons under 18 years of age without recommendation from a health care professional. There is limited experience of treating this age group with Nicorette Invisi Patch.

Use of the patch beyond 6 months is generally not recommended. Some ex-smokers may need longer treatment to avoid returning to smoking.

How to apply the patches

Nicorette Invisi Patch should be applied to clean, dry intact areas of hairless skin, for example on the hip, upper arm, or chest. These areas should be varied each day and the same site should not be used on consecutive days.

1 Wash your hands before applying the patch.
2 Cut open the pouch with scissors along the side, as indicated. Select a clean, dry, hairless intact area of skin, such as the hip, upper arm or chest.
3 Peel one part of the silvery aluminum backing away as far as possible. Avoid touching the sticky surface of the patch with your fingers, as far as possible
4 Apply the sticky part of the patch carefully onto the skin and peel off the remaining half of the silvery aluminum backing.
5P ress the patch firmly onto the skin with your palm or finger-tips.
6 Rub your fingers firmly round the edge to ensure that the patch sticks firmly.

After removal, used patches should be disposed of carefully.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Use in non-smokers.

4.4 Special warnings and precautions for use

The benefits of quitting smoking outweigh any risks associated with correctly administered nicotine replacement therapy (NRT).

A risk-benefit assessment should be made by an appropriate healthcare professional for patients with the following conditions:

- Cardiovascular disease: Dependent smokers with a recent myocardial infarction, unstable or worsening angina including Prinzmetal's angina, severe cardiac arrhythmias, recent cerebrovascular accident, and/or who suffer with uncontrolled hypertension should be encouraged to stop smoking with non-pharmacological interventions (such as counselling). If this fails, Nicorette Invisi Patch may be considered but as data on safety in this patient group are limited, initiation should only be under close medical supervision.

- Diabetes Mellitus. Patients with diabetes mellitus should be advised to monitor their blood sugar levels more closely than usual when smoking is stopped and NRT is initiated, as reductions in nicotine-induced catecholamine release can affect carbohydrate metabolism.
- 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.
- Gastrointestinal Disease: Nicotine may exacerbate symptoms in patients suffering from oesophagitis, gastric or peptic ulcers and NRT preparations should be used with caution in these conditions.
- *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 (see section 4.8).

Patients with chronic dermatological disorders such as psoriasis, chronic dermatitis or urticaria should not apply Nicorette Invisi Patch to the affected areas. Erythema may occur. If it is severe or persistent, treatment should be discontinued.

Danger in children: Doses of nicotine tolerated by smokers can produce severe toxicity in children that may be fatal. Products containing nicotine should not be left where they may be handled or ingested by children, see section 4.9 Overdose.

Transferred dependence: Transferred dependence can occur but is unusual and both less harmful and easier to break than smoking dependence.

Nicorette Invisi Patch should be removed prior to undergoing any Magnetic Resonance Imaging (MRI) procedures to prevent the risk of burns.

4.5 Interaction with other medicinal products and other forms of interaction

Smoking (but not nicotine) is associated with an increase in CYP1A2 activity. After cessation of smoking, reduced clearance of substrates for this enzyme may occur. This may lead to an increase in plasma levels for some medicinal products of potential clinical importance and for products with a narrow therapeutic window, e.g. theophylline, tacrine, clozapine and ropinirole

The plasma concentration of other drugs metabolised in part by CYP1A2 e.g. imipramine, olanzapine, clonipramine and fluvoxamine may also increase on cessation of smoking, although data to support this are lacking and the possible clinical significance of this effect is unknown.

Limited data indicate the metabolism of flecainide and pentazocine may also be induced by smoking.

Nicotine may possibly enhance the haemodynamic effects of adenosine i.e. increase in blood pressure and heart rate and also increased pain response (angina-pectoris type chest pain) provoked by adenosine administration.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/ contraception in males and females
In contrast to the well-known adverse effects of tobacco smoking on human conception and pregnancy, the effects of therapeutic nicotine treatment are unknown. Thus, whilst to date no specific advice regarding the need for female contraception has been found to be necessary, the most prudent state for women intending to become pregnant is to be both non-smoking, and not using NRT.

Whilst smoking may have adverse effects on male fertility, no evidence exists that particular contraceptive measures are required during NRT treatment by males.

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.

Nicotine passes freely to the foetus and affects its breathing movements and circulation. The effect on the circulation is dose-dependent.

Therefore, the pregnant smoker should always be advised to stop smoking completely without the use of nicotine replacement therapy. The risk of continued smoking may pose a greater hazard to the foetus as compared with the use of nicotine replacement therapy products in a supervised cessation programme. Use of Nicorette Invisi Patch should only be initiated after advice from a physician.

Lactation:
Nicotine passes freely into breast milk in quantities that may affect the child even in therapeutic dose. Nicorette Invisi Patch should therefore be avoided during breast-feeding.
Should smoking cessation not be achieved, use of the Nicorette Invisi Patch by breast feeding smokers should only be initiated after advice from a health care professional.

Fertility
In females tobacco smoking delays time to conception, decreases in-vitro fertilization success rates, and significantly increases the risk of infertility.
In males tobacco smoking reduces sperm production, increases oxidative stress, and DNA damage. Spermatozoa from smokers have reduced fertilizing capacity.
The specific contribution of nicotine to these effects in humans is unknown.

4.7 Effects on ability to drive and use machines

Nicorette Invisi Patch has no or negligible influence on the ability to drive and use machines

4.8 Undesirable effects

Effects of Smoking Cessation

Regardless of the means used, a variety of symptoms are known to be associated with quitting habitual tobacco use. These include emotional or cognitive effects such as dysphoria or depressed mood; insomnia; irritability, frustration or anger; anxiety; difficulty concentrating, and restlessness or impatience.

There may also be physical effects such as decreased heart rate; increased appetite or weight gain, dizziness or presyncopal symptoms, cough, constipation, gingival bleeding or aphthous ulceration, or nasopharyngitis. In addition, and of clinical significance, nicotine cravings may result in profound urges to smoke.

Adverse drug reactions

Nicorette Invisi Patch may cause adverse reactions similar to those associated with nicotine administered by other means and are mainly dose dependent.

About 20% of users experienced mild local skin reactions, during the first weeks of treatment. Allergic reactions (including symptoms of anaphylaxis) occur rarely during use of Nicorette Invisi Patch.

Most of the undesirable effects reported by the subjects occur during the early phase of treatment and are mainly dose dependent.

The adverse reactions observed in patients treated with nicotine patch formulations during clinical trials and post-marketing experience are listed below by system organ class (SOC).

Frequencies are provided according to the following convention:
Very common (>1/10); common (> 1/100, <1/10); uncommon (>1/1 000, < 1/100); rare (>1/10 000, < 1/1 000); very rare (<1/10 000), Not known (cannot be estimated from the available data). ** Frequency category estimated using the "Rule of 3"

Body System	**Incidence***	**Reported adverse event (Preferred Term)**
Immune system disorder	Uncommon	Hypersensitivity [a#]
	Rare**	Anaphylactic reaction[a]
Nervous system disorder	Common	Headache[a§]
	Uncommon	Paraesthesia[a#]
	Not known	Seizure**
Cardiac disorders	Uncommon	Palpitations [a]
	Uncommon	Tachycardia [a]
Vascular disorders	Uncommon	Flushing [a]
	Uncommon	Hypertension [a]
Respiratory, Thoracic and Mediastinal Disorders	Uncommon	Dyspnoea [a]
Gastrointestinal disorders:	Common	Nausea [a§]
	Common	Vomitting[a]
	Rare	Gastrointestinal discomfort[b] and/or pain
Skin and subcutaneous tissue disorders:	Very common	Pruritus
	Common	Rash[a]
	Common	Urticaria[a]
	Uncommon	Hyperhidrosis[a]
	Rare**	Angioedema[a]
	Rare	Erythema[a]
Musculoskeletal and Connective Tissue Disorders	Uncommon	Myalgia [b]
	Rare **	Pain in extremity
General disorders and administration site conditions:	Uncommon	Application site reactions
	Uncommon	Asthenia [a]
	Uncommon	Chest discomfort and pain [a]
	Uncommon	Malaise [a]
	Uncommon	Fatigue [a#§]

[a] systemic effects; [b]In vicinity/region of patch

Although the frequency is <1% the PT occurred at a frequency ≥1% in another formulation in which the PT was identified as a systemic ADR.
§ Although the frequency in the active group is less than that of the placebo group, the frequency in the specific formulation in which the PT was identified as a systemic ADR was greater in the active group than the placebo group.
** Cases of seizures have been reported in subjects taking anti-convulsant therapy or with a history of epilepsy.

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, website: www.hpra.ie.

4.9 Overdose

Excessive use of nicotine from either NRT and/or smoking might cause symptoms of an overdose. Symptoms of overdose are those of acute nicotine poisoning and include nausea, salivation, abdominal pain, diarrhoea, sweating, headache, dizziness, disturbed hearing and marked weakness. At high doses, these symptoms may be followed by hypotension, weak and irregular pulse, breathing difficulties, prostration, circulatory collapse and general convulsions.

Doses of nicotine that are tolerated by adult smokers during treatment may produce severe symptoms of poisoning in children and may prove fatal.Suspected nicotine poisoning in a child should be considered a medical emergency and treated immediately.

Management of overdose
The administration of nicotine must be stopped immediately and the patient should be treated symptomatically. Remove patch and rinse application site with water.
Oral activated charcoal reduces gastrointestinal absorption of nicotine. Tachycardia causing circulatory impairment may require treatment with a β blocker. Excitation and convulsions may be treated with diazepam. Mechanically assisted ventilation should be instituted if necessary.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drug for treatment of addiction.
ATC code: N07B A01

Abrupt cessation of the use of tobacco-containing products following a prolonged period of daily use results in a characteristic withdrawal syndrome that includes four or more of the following: dysphoria or depressed mood; insomnia; irritability, frustration or anger; anxiety; difficulty concentrating, restlessness or impatience; decreased heart rate; and increased appetite or weight gain. Nicotine craving, which is recognised as a clinically relevant symptom, is also an important element in nicotine withdrawal.

Clinical studies have shown that nicotine replacement products can help smokers abstain from smoking.

5.2 Pharmacokinetic properties

The patches are labelled by the average amount of nicotine released over 16 hours.
A linear relationship exists between released amount of nicotine (dose) and plasma levels of nicotine over the therapeutic dose range, 10-25 mg/16 hours. The mean peak plasma levels of nicotine (C_{max}) achieved are calculated to:

Dose nicotine (mg/16 hours)	C_{max} (ng/ml)
10	10
15	15.5
25	26.5

The calculated peak plasma levels are in the same range as true measured peak plasma concentrations: 11 ng/mL for the 10 mg patch and 25 ng/mL for the 25 mg patch. Interpolation yields a peak plasma concentration of 16 ng/mL for the 15 mg patch.
The maximum level of plasma concentration after administration is reached after approximately 9 hours (t_{max}). The plasma peak is in the afternoon/ evening when the risk of relapse is highest.

The volume of distribution of nicotine is about 2 to 3 L/kg and the half-life approximately 3 hours. The major eliminating organ is the liver, and average plasma clearance is about 70 L/hour. The kidney and lung also metabolise nicotine. More than 20 metabolites of nicotine have been identified, all of which are believed to be less active than the parent compound.

Plasma protein binding of nicotine is less than 5%. Therefore, changes in nicotine binding from use of concomitant drugs or alterations of plasma proteins by disease states would not be expected to have significant effects on nicotine kinetics.

The primary metabolite of nicotine in plasma, cotinine, has a half-life of 15 to 20 hours and concentrations that exceed nicotine by 10-fold.

The primary urinary metabolites are cotinine (12% of the dose) and trans-3-hydroxy-cotinine (37% of the dose). About 10% of nicotine is excreted unchanged in the urine.

Progressive severity of renal impairment is associated with decreased total clearance of nicotine. Raised nicotine levels have been seen in smoking patients undergoing hemodialysis.

The pharmacokinetics of nicotine is unaffected in cirrhotic patients with mild liver impairment (Child score 5) and nicotine clearance is decreased in cirrhotic patients with moderate liver impairment (Child score 7).

A minor reduction in total clearance of nicotine has been demonstrated in healthy elderly patients, however, not justifying adjustment of dosage.

Plasma nicotine concentrations show dose proportionality for the three patch doses.

5.3 Preclinical safety data

Non-clinical studies with Nicorette Invisi Patch support the well established safety of nicotine use in NRT and documented safety profile for the excipients.

There is no clear evidence of nicotine being genotoxic or mutagenic. The well established carcinogenicity of tobacco smoke is mainly related to substances formed by the pyrolysis of tobacco. None of these occur in nicotine patch.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Backing Layer
Polyethylene terephthalate film (PET)

Nicotine Matrix
Triglycerides, medium-chain
Basic butylated methacrylate copolymer Acrylate Matrix
Acrylic adhesive solution
potassium hydroxide
croscarmellose sodium
aluminium acetylacetonate

Release Liner
Polyethylene terephthalate film (PET) film single side aluminised, both sides siliconised.

Printing Ink Solution
blending varnish, printing ink beige, printing ink brown

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25°C

6.5 Nature and contents of container

Heat-sealed multilaminate pouch containing one patch. The pouch material consists of paper, adhesive, polyethyelene terephthalate film, aluminium, and either polyacrylinitrile-copolymer or cyclo olefine copolymer coextrudate.
Cartons of 1,2,3,5,7 and 14 patches.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Nicotine residues in used patches may present a hazard to children and pets, thus used patches should be folded, sticky sides together, put back in an empty pouch and placed in household rubbish.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA23490/019/007

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 5th September 2008

Date of last renewal: 5th September 2013

10 DATE OF REVISION OF THE TEXT

December 2023