Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Nicotinell TTS 20, 14mg/24 hours Transdermal Patch

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each patch contains 35mg S (-) nicotine, average absorption rate 14mg in 24 hours.
Drug releasing surface area – 20cm^2

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Transdermal patch.
Transdermal therapeutic system, consisting of a round, flat, matrix-type self-adhesive yellowish-ochre coloured patch printed 'CG FEF' on the patch surface. It is protected by a rectangular metallic release liner backing to be discarded before application.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

The treatment of nicotine dependence, as an aid to smoking cessation.

4.2 Posology and method of administration

Method of administration
Nicotinell TTS should be used as soon as it has been removed from the child-resistant pouch. Following removal of the metallic backing, the Nicotinell TTS patch should be applied to an area of dry skin with no skin lesions and little hair on the trunk or upper arm and held in position for 10-20 seconds with the palm of the hand. It should not be applied to skin that is red, broken or irritated. Each patch should be removed after 24 hours and disposed of safely (see "Warnings"). A different site of application should be chosen each day and 7 days should be allowed to elapse before a new patch is applied to the same area of skin to avoid risk of local irritation. During handling, avoid contact with the eyes and nose and wash your hands after application. After removal, used patches should be disposed of carefully and kept out of the sight and reach of children.

The dosage must not be adjusted by cutting a patch.

Adults over 18 years and the elderly

Abrupt cessation of smoking
Users should stop smoking completely during treatment with Nicotinell TTS.

Sizes of 30cm^2, 20cm^2 and 10cm^2 are available to permit gradual withdrawal of nicotine replacement, using treatment periods of 3-4 weeks for each size.

For smokers of more than 20 cigarettes a day:

	Dose	**Duration**
Step 1	Nicotinell TTS 30 (21mg/24h)	First 3-4 weeks
Step 2	Nicotinell TTS 20 (14mg/24h)	Next 3-4 weeks
Step 3	Nicotinell TTS 10 (7mg/24h)	Last 3-4 weeks

For smokers of less than 20 cigarettes a day:

	Dose	**Duration**
Step 2	Nicotinell TTS 20 (14mg/24h)	Next 3-4 weeks
Step 3	Nicotinell TTS 10 (7mg/24h)	Last 3-4 weeks

The strength of patch may be adjusted according to individual response, maintaining or increasing the dose if abstinence is not achieved or if withdrawal symptoms are experienced. Total treatment periods of more than 3 months and daily doses above 30cm2 have not been evaluated. The treatment is designed to be used continuously for 3 months but not beyond. However, if abstinence is not achieved at the end of the 3 month treatment period, further treatments may be recommended following a re-evaluation of the patient's motivation.

Nicotine transdermal patch should not be used for more than 12 months unless the potential benefit outweighs the potential risk to the smokers.

Children and Adolescent (aged 12-17 years of age)
Nicotinell TTS should not be administered to persons under 18 years of age without recommendation from a physician.

Children below 12 years of age:
Nicotine patches are not recommended for use in children under 12 years.

Elderly
Experience in the use of Nicotinell TTS in smokers over the age of 65 years is limited. Nicotinell TTS does not appear to pose safety problems in this age group.

Hepatic and Renal Impairment
Use with caution in patients with moderate to severe hepatic or renal impairment as the clearance of nicotine or its metabolites may be decreased with the potential for increased adverse effects.

Potential for abuse and dependence
Transdermal nicotine is likely to have a very low abuse potential because of its slow onset of action, low fluctuations in blood concentrations, inability to produce high blood concentrations of nicotine, and the infrequent (once daily) use. Moreover, gradual weaning from Nicotinell TTS is instituted within the treatment schedule, and the risk of dependence after therapy is minimal. The effects of abrupt withdrawal from Nicotinell TTS are likely to be similar to those observed with tobacco withdrawal from comparable nicotine concentrations.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Cardiovascular disease
Dependent smokers with a recent myocardial infarction, severe cardiac arrhythmias, or recent cerebrovascular accident who are considered to be haemodynamically unstable should be encouraged to stop smoking with non-pharmacological interventions (such as counseling). If this fails, Nicotinell may be considered but as data on safety in these patient groups are limited, initiation should only be under close medical supervision. If there is a clinically significant increase in cardiovascular or other effects attributable to nicotine, the nicotine patch dose should be reduced or discontinued.

Diabetes
Blood glucose levels may be more variable during smoking cessation, with or without NRT, so it is important for diabetics to closely monitor their blood glucose levels while using this product.

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.

Warnings

Nicotine is a toxic drug and milligram doses are potentially fatal if rapidly absorbed. Treatment with Nicotinell TTS should be discontinued if symptoms of nicotine overdosage appear. Mild intoxication produces nausea, vomiting, abdominal pain, diarrhoea, headache, sweating and pallor (see 'Overdosage').

Danger in small children

Doses of nicotine that are tolerated by adult smokers during treatment can produce severe symptoms of poisoning in small children and may prove fatal. Both before and after use, Nicotinell TTS contains a significant amount of nicotine. Subjects must be cautioned that the patches must not be handled casually or left where they might be inadvertently misused or consumed by children. Used patches must be disposed of with care by folding them in half with the adhesive sides inwards and ensuring they are out of the sight and reach of children and pets.

Precautions:

Users should stop smoking completely during therapy with Nicotinell TTS. They should be informed that if they continue to smoke while using Nicotinell TTS, they may experience increased adverse effects due to the hazards of smoking, including cardiovascular effects.

In subjects with the conditions listed below, Nicotinell TTS should only be used following a careful risk-benefit assessment, and only in cases where subjects have found it impossible to stop smoking without use of Nicotinell TTS:
-Diabetes mellitus
-Severe hepatic and/or renal impairment - (see Dosage and Administration).

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

Nicotinell TTS should be used with caution on diseased skin (see section 4.2). Patients with a history of dermatitis are more likely to experience generalised skin reactions or localized erythema, swelling or rash that lasts longer than 4 days. In the event of a severe or persistent skin reactions treatment should be discontinued and another pharmaceutical form of nicotine replacement therapy should be considered taking into account the expected benefit and the potential risk to the patient.

Nicotinell TTS contains aluminium. The patch should therefore be removed prior to undergoing any MRI (Magnetic Resonance Imaging), defibrillation or cardioversion procedures.

Contact sensitisation was reported in a few patients using transdermal nicotine in clinical trials. Patients who develop contact sensitisation to nicotine should be cautioned that a severe reaction could occur from smoking or exposure to other nicotine containing products.

4.5 Interaction with other medicinal products and other forms of interaction

No information is available on interactions between Nicotinell TTS and other drugs.

Smoking, but not nicotine, is associated with increased CYP1A2 activity. Cessation of smoking, with or without nicotine replacement, may alter the individual's response to concomitant medication and may require adjustment of dose. Smoking is thought to increase the metabolism through enzyme induction and thus to lower the blood concentrations of drugs such as antipyrine, caffeine, oestrogens, desmethyldiazepam, imipramine, lignocaine, oxazepam, pentazocine, phenacetin, theophylline, warfarin, ropinirole, clozapine and olanzapine. Cessation of smoking may result in increased concentrations of these drugs and may require adjustment.

4.6 Fertility, pregnancy and lactation

Pregnancy

Patients should be advised to give up smoking without the use of nicotine replacement therapy. Should this fail, a medical assessment of the risk benefit of Nicotinell TTS should be made. Quitting smoking, with or without nicotine replacement therapy, is not to be considered in isolation but in the context of overall management, taking into account the psychological and sociological context and any other associated substance dependencies.

Teratogenicity studies with nicotine in several animal species have demonstrated non-specific retardation of foetal growth. Studies in pregnant rats have indicated the presence of behavioural disorders in the offspring, and in the mouse the unborn

offspring of animals treated with approximately 120 times the human transdermal dose showed skeletal defects in the peripheral parts of the limbs. Embryo implantation in rats and rabbits may be inhibited or delayed by nicotine.

Smoking by pregnant women can be the cause of delayed intra-uterine growth, in utero foetal death, premature birth and neonatal hypotrophy, which appear to be correlated with the extent of tobacco exposure during pregnancy as these effects are observed when tobacco exposure is continued during the third trimester.

The nicotine provided by substitution treatment is not without adverse reactions on the foetus, as evidenced by the haemodynamic impact observed in the third trimester (e.g. changes in heart rate), which may affect the foetus close to birth. However, the risk for the foetus is probably less than to be expected with continued smoking due to:
-Lower maximal plasma concentrations compared to inhaled nicotine resulting in a nicotine exposure less or not more than associated with smoking.
-No exposure to polycyclic hydrocarbons and carbon monoxide

Breast-feeding
Nicotine is excreted in breast milk in quantities that may affect the child even in therapeutic doses. Nicotine replacement therapy products, like smoking itself, should therefore be avoided during breast-feeding. Should smoking withdrawal not be achieved, use of oral forms should be preferred compared with patches. The use of the patch by breast-feeding smokers should only be initiated after advice from a doctor. However the use of any form of nicotine replacement therapy in breast-feeding women should be initiated only if the expected benefits to the nursing mother outweigh the potential risks to the infant.

Fertility
Overall, there are no clear cut grounds for believing that nicotine at the concentrations reached by treatment with Nicotinell TTS has any teratogenic potential and/or inhibitory effects on fertility.

4.7 Effects on ability to drive and use machines

When Nicotinell TTS is used as recommended, there are minimal risks for driving vehicles or operating machinery. Nevertheless, one should take into consideration that smoking cessation can cause behavioural changes.

4.8 Undesirable effects

In principle, Nicotinell TTS can cause adverse reactions similar to those associated with nicotine administered by other means (including smoking). Since the maximum plasma concentrations of nicotine that are produced by Nicotinell TTS are lower than those produced by smoking and fluctuate less, nicotine-related adverse reactions occurring during treatment with Nicotinell TTS can be expected to be less marked than during smoking.

Some of the symptoms listed below are hard to differentiate from recognised tobacco withdrawal symptoms when comparison with placebo is made. The placebo used contained about 13% of the nicotine of a matching Nicotinell TTS (to match colour and odour for blinding purposes).

The main unwanted effect of Nicotinell TTS is application site reaction. This led to premature discontinuation of Nicotinell TTS in about 6% of clinical trial participants. Skin reactions consisted of erythema or pruritus at the patch site. Oedema, burning sensation, blisters, rash, or pinching sensation at the application site was also noted. The majority of these reactions were mild. Most of the skin reactions resolved within 48 hours, but in more severe cases the erythema and infiltration lasted from 1 to 3 weeks. The time of onset of significant skin reactions was between 3 and 8 weeks from the start of therapy. In isolated cases the skin reactions extended beyond the application sites. Isolated cases of urticaria, angioneurotic oedema and dyspnoea were reported.

Upper respiratory tract infection and cough reported as adverse reactions may be linked to a chronic bronchitis induced by long term smoking in the past

Aphthous stomatitis may develop in connection with smoking cessation, but any relation with the nicotine treatment is unclear.

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.

Clinical trial data and Post Marketing data

The following convention has been utilised for the classification of adverse reactions:

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); very rare (<1/10,000), or not known (cannot be estimated from available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

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

System Organ Class	**Adverse Reaction**	**Frequency**
Immune system disorder	allergic reactions such as urticaria, rash and pruritus; angioedema and anaphylactoid reaction	Not Known
	hypersensitivity*	Uncommon
	anaphylactic reactions	Very Rare
Psychiatric disorders*:	sleep disorders including insomnia, abnormal dreams	Very Common
	agitation, anxiety, nervousness	Common
	disturbance in attention, somnolence, affect lability, irritability, depressed mood and confusional state	Uncommon
Nervous system disorders*	, tremor	Common
	paraesthesia, dysgeusia and blurred vision	Uncommon
Cardiac disorders	palpitations	Common
	, tachycardia	Uncommon
	dyspnea and arrhythmia	Rare
Respiratory, thoracic and mediastinal disorders	cough, pharyngitis, dyspnoea	Common
Gastrointestinal disorders*	nausea, vomiting	Very Common
	abdominal pain, upper dyspepsia, diarrhoea, dry mouth, constipation	Common
	flatulence	Uncommon
Skin and subcutaneous tissue disorders	sweating increased	Common
	hyperhydrosis	Uncommon
	dermatitis allergic*, dermatitis contact*, photosentivity	Very Rare
Musculoskeletal, connective tissue and bone disorders	myalgia	Common
	arthralgia	Uncommon
General disorders and administration site conditions	application site reactions**	Very common
	application site pain, asthenia, fatigue	Common
	malaise, influenza type illness, asthenic conditions, pain and discomfort	Uncommon

*Symptoms may be ascribed also to withdrawal symptoms in connection with smoking cessation and may be due to insufficient replacement of nicotine.

**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.

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, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

The toxicity of nicotine cannot be directly compared with that of smoking, because tobacco smoke contains additional toxic substances (eg carbon monoxide, and tar). Chronic smokers can tolerate doses of nicotine that, in a non-smoker, would be more toxic, because of the development
of tolerance.

Even small quantities of nicotine are dangerous in children, and may result in severe symptoms of poisoning which may prove fatal. If poisoning is suspected in a child, a doctor must be consulted immediately.

Application of several Nicotinell TTS patches could result in serious overdosage. Slower absorption after cutaneous exposure to nicotine favours the development of tolerance to toxic effects.

Rapid systemic delivery of nicotine from Nicotinell TTS would not be expected on chewing and swallowing, owing to the slow release of nicotine from the patch and first-pass metabolism.

Symptoms
Signs and symptoms of overdosage would be the same as those of acute nicotine poisoning. In non-smoking children and adults, these include pallor, sweating, hyperhidrosis, salivation, vomiting, dyspnea, abdominal cramps, diarrhoea, headache, dizziness, hearing and vision disturbances, tremor, mental confusion, cardiac arrythmia, muscle weakness, convulsions, prostration, absence of neurological reaction, circulatory collapse and respiratory failure. Lethal doses may produce convulsions, and death follows as a result of peripheral or central respiratory paralysis, or, less frequently, cardiac failure.

Treatment of overdose
If the patient shows signs of overdosage, Nicotinell TTS should be removed immediately. The skin surface may be washed with water and dried (no soap should be used as it will increase nicotine absorption). The skin will continue to deliver nicotine into the blood stream for several hours after removal of the system, possibly because of a depot of nicotine in the skin.

Overdose from Ingestion
All nicotine intake should stop immediately and the patient should then be treated symptomatically and all vital signs monitored. Other treatment measures for acute nicotine poisoning include artificial respiration in the case of respiratory paralysis, maintaining normal body temperature, and treatment of hypotension and cardiovascular collapse.

Each Nicotinell TTS patch is sealed in a child-resistant sachet and the product must be kept out of the reach of children at all times (see "Section 4.4 Special Warnings and Precautions for Use"). Even doses of nicotine which are tolerated by adults during treatment with Nicotinell TTS could produce severe symptoms of poisoning in small children following accidental application, and may prove fatal.

Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: drugs used in nicotine dependence, ATC code: N07BA01. Mechanism of action and pharmacodynamic properties:
Mode of action: S(-)-nicotine is the most pharmacologically active form of nicotine, the major alkaloid of tobacco. S(-)-nicotine acts primarily on cholinergic receptors of the nicotinic type in the peripheral and central nervous system. For many effects, low doses of S(-)-nicotine have a stimulant action, and high doses a depressant effect. Intermittent administration of S(-)-nicotine affects neurohormonal pathways, and results in the release of acetylcholine, noradrenaline,

dopamine, serotonin, vasopressin, beta-endorphin, growth hormone, cortisol and ACTH. These neuroregulators may be involved in the reported behavioural and subjective effects of smoking.

Quitting smoking abruptly after prolonged, daily consumption induces a withdrawal syndrome consisting of at least four of the following symptoms: dysphoria or depressive mood, insomnia, irritability, feelings of frustration or anger, anxiety, difficulty concentrating, agitation or impatience, slowed cardiac rhythm, increased appetite and weight gain. The craving for nicotine is considered as a recognized clinical symptom of the withdrawal syndrome.

Nicotine replacement is an established therapy as an aid to smoking cessation. Nicotinell TTS provides for a convenient once daily administration by exploiting the fact that S(-)-nicotine is readily absorbed through the skin into the systemic circulation. Placebo-controlled, double-blind studies have shown that nicotine replacement with Nicotinell TTS produces smoking abstinence rates statistically significantly better than placebo, with or without group support. There was also a strong trend towards reduction of withdrawal symptoms.

Application of Nicotinell TTS 20 to smokers abstinent overnight resulted in small increases in mean heart rate and systolic blood pressure and a decrease in stroke volume. The effects were smaller in magnitude than those produced by cigarette smoking.

5.2 Pharmacokinetic properties

Absorption
Nicotine is directly absorbed through the skin and enters the systemic circulation.

Following single application of Nicotinell TTS to the skin of healthy abstinent smokers there is an initial 1-2 hours delay followed by a progressive rise in nicotine plasma concentrations, with a plateau attained at about 8-10 hours after application.

Following withdrawal of the patch, plasma nicotine levels fall more slowly than would be expected, given the plasma elimination half-life of nicotine (after intravenous administration: 2 hours).

The probable existence of a cutaneous deposit explains why about 10% of the nicotine reaching the blood derives from the skin after patch withdrawal. The absolute bioavailability of the patch, compared to intravenous nicotine perfusion, is about 77%.

In the majority of subjects the area under the plasma concentration curve (AUC 0-24 hours) increases approximately in proportion to the dose of nicotine delivered by the patch. Nicotinell TTS is designed to deliver approximately 0.7mg/cm2/24 hours. In comparison with an i.v. infusion, 76.8% of the nicotine released from Nicotinell TTS is systemically available. Steady state plasma concentrations after repeated daily administration are within the range observed during moderate cigarette smoking.

Absorption of nicotine over 24 hours varies by a factor of two between different individuals; however within-individual variability is small indicating consistent performance of the transdermal system.

Distribution
S(-)-nicotine is distributed widely in the body with a volume of distribution of approximately 180 litres. Nicotinell TTS crosses the blood-brain barrier, placenta and is detectable in breast milk. The plasma protein binding is only 5%.

Elimination
Total plasma clearance of nicotine ranges from 0.92 to 2.43 litres/min. It is eliminated mainly via hepatic metabolism and the main metabolites are cotinine and nicotine 1-N-oxide. The renal elimination of unchanged nicotine is pH-dependent and minimal in the event of an alkaline urinary pH.

Nicotine is excreted in breast milk.

5.3 Preclinical safety data

Nicotine produced equivocal results in in vitro genotoxicity tests. Nicotine was negative in in vivo tests. In reproductive toxicity studies, nicotine was shown to induce post-implantation loss and reduce the growth of foetuses. Results from carcinogenicity studies did not provide any clear evidence of a tumorigenic effect of nicotine.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Acrylate esters vinylacetate co-polymers
Fractionated coconut oil
Methacrylic acid esters co-polymers
Aluminized polyester backing film
Aluminized and siliconized polyester film release liner

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

Each Nicotinell TTS patch is sealed in a:

Child resistant sachet composed of heat-sealed paper / aluminium / polyamide / polyacrylnitrile

or

Child resistant sachet composed of heat-sealed paper / Polyethylene terephthalate/Aluminium/Cyclo olefine copolymer coextrudate enclosed in a cardboard carton

The sachets are packed in a cardboard carton:

Pack sizes: 2, 3, 7, 14, 21, 28 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

Used patches must be disposed of with care by folding them in half with the adhesive sides inwards and ensuring they are out of the sight and reach of children and pets.

7 MARKETING AUTHORISATION HOLDER

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Claude Debussylaan 10
Amsterdam
Noord-Holland
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