1 NAME OF THE MEDICINAL PRODUCT

Nicotinell TTS 20

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Nicotinell TTS 20 patch contains 35mg S(-)-nicotine which provides an average absorption rate of 14 mg nicotine in 24 hours.

3 PHARMACEUTICAL FORM

Transdermal patch.

The Nicotinell TTS patch is a transdermal therapeutic system, consisting of a round, flat, matrix-type self-adhesive, yellowish-ochre coloured patch. It is protected by a rectangular metallic release liner backing to be discarded before application.

Nicotinell TTS 20 patch 14mg/24 hour has a drug releasing area of 20 cm^2 and is printed CG FEF on the patch surface.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Nicotinell patches relieve and/or prevent cravings and nicotine withdrawal symptoms associated with tobacco dependence. They are indicated to aid smokers wishing to quit or reduce prior to quitting, to assist smokers who are unwilling or unable to smoke, and as a safer alternative to smoking for smokers and those around them.

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

Nicotinell patches should preferably be used in conjunction with a behavioural support programme.

4.2 Posology and method of administration

Method of administration

The patch should be used as soon as it has been removed from the child-resistant pouch. Following removal of the metallic backing, the patch should be applied to an area of dry skin with no skin lesion and little hair (shoulder blade, hip, lateral surface of the arms, etc.) 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 and kept out of the sight and reach of children (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.

The dosage must not be adjusted by cutting a patch.

Use for 24 hours optimizes the effect against morning cravings but in pregnant patients, it is recommended that the patch is removed before going to bed (see section 4.6)

During handling, avoid contact with the eyes and nose and wash your hands after application.

Adults over 18 years and the elderly

Abrupt cessation of smoking

Users should stop smoking completely during treatment with nicotine patches.

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 $30cm^2$ 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.

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 Adolescents (aged 12-17 years of age):
Adolescents (12-17 years) should seek medical advice before using the product. Adolescents should follow the schedule of treatment for abrupt cessation of smoking as given above but as data are limited in this age group, medical advice should be obtained should it be found

necessary to use the patch beyond 10 weeks. The use of NRT in adolescents should only be used when the benefits of abstinence outweigh the risks of continued smoking.

Children below 12 years of age:

Nicotine patches are not recommended for use in children under 12 years.

Elderly:

Experience in the use of these patches 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 (see also section 4.4 *Transferred Dependence*) 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 the patches 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

Nicotinell TTS should not be administered to non-smokers or occasional smokers. The system is contraindicated in diseases of the skin which may complicate patch therapy, and known hypersensitivity to nicotine or any of the components of the patch listed in section 6.1.

4.4 Special warnings and precautions for use

Any risks that may be associated with nicotine replacement therapy are substantially outweighed by the well-established dangers of continued smoking.

Precautions:

Users should be informed that if they continue to smoke while using the patches, they may experience increased adverse effects due to the hazards of smoking, including cardiovascular effects.

Nicotinell TTS should be used with caution on diseased skin (see section 4.2). In the event of a severe or persistent skin reaction, discontinue treatment and use another pharmaceutical form of nicotine replacement therapy.

Cardiovascular disease

In stable cardiovascular disease Nicotinell TTS presents a lesser hazard than continuing to smoke. However dependent smokers currently hospitalized as a result of a recent myocardial infarction, unstable or worsening angina pectoris including Prinzmetal's angina, severe cardiac arrhythmias, uncontrolled hypertension or recent cerebrovascular accident and who are considered to be haemodynamically unstable should be encouraged to stop smoking with

non-pharmacological interventions (such as counselling). If this fails, Nicotinell TTS may be considered but as data on safety in this patient group are limited, initiation should only be under 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.

Dermatitis

Patients with a history of dermatitis are more likely to experience generalised skin reactions or localized erythema, swelling or rash. In this case a decision must be made whether to discontinue and another pharmaceutical form of nicotine replacement therapy should be considered.

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.

Diabetes mellitus

Patients with diabetes mellitus should be advised to monitor their blood sugar levels more closely than usual when nicotine replacement therapy is initiated as catecholamines released by nicotine can affect carbohydrate metabolism and the blood glucose levels may be more variable during smoking cessation, with or without NRT.

Allergic reactions

Discontinuation of treatment may be advisable in cases of severe or persistent allergic reactions.

Angioedema and urticaria have been reported. 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.

Renal and or hepatic impairment

Should be used in caution in patients with moderate to severe hepatic impairment and/or severe impairment as the clearance of nicotine or its metabolites may be decreased with the potential for increased adverse effects (See Dosage and Administration).

Gastro-Intestinal disease

Nicotinell TTS should be used with caution in patients suffering from active

oesophagitis, oral and pharyngeal inflammation, gastritis, gastric ulcer or peptic ulcers as their symptoms may be exacerbated.

Pheochromocytoma and uncontrolled hyperthyroidism

Nicotinell TTS should be used with caution in patients with uncontrolled hyperthyroidism or pheochromocytoma as nicotine causes release of catecholamines.

Transferred dependence

Transferred dependence is rare and is both less harmful and easier to break than smoking dependence.

Danger in small children

Nicotine is a toxic substance. Doses of nicotine that are tolerated by adult and adolescent smokers can produce severe toxicity in small children that may be fatal (see section 4.9). Both before and after use, the patch 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 that they do not fall into the hands of children under any circumstances. Patches should be kept out of the sight and reach of children.

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

Stopping smoking
When a smoker stops, this may result in slower metabolism and a consequent rise in blood levels of such drugs.

4.5 Interaction with other medicinal products and other forms of interaction

Polycyclic aromatic hydrocarbons in tobacco smoke induce the metabolism of drugs catalysed by CYP 1A2 (and possibly by CYP 1A1).

No information is available on interactions between Nicotinell TTS and other drugs. 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. Smoking cessation itself may require adjustment of some drug therapy.

4.6 Fertility, pregnancy and lactation

Pregnancy

Adverse reproductive and developmental effects have been reported following exposure to tobacco and nicotine during pregnancy. Women who are pregnant should first be advised to stop smoking without the assistance of nicotine replacement therapy. Stopping smoking is the single most effective intervention for improving the health of both the pregnant smoker and her baby, and the earlier abstinence is achieved the better. However, if the mother cannot (or is considered unlikely to) quit without pharmacological support, NRT may be used as the risk to the foetus is lower than that expected with smoking tobacco. Stopping completely is by far the best option but Nicotinell patches may be used in pregnancy as a safer alternative to smoking and should only be used if the expected benefits to the mother outweigh the potential risks to the foetus. Because of the potential for nicotine-free periods, intermittent dose forms are preferable, but patches may be necessary if there is significant nausea and/or vomiting. If patches are used they should, if possible, be removed at night when the foetus would not normally be exposed to nicotine.

Breast-feeding

Nicotine is excreted in breast milk. Nicotine replacement therapy should therefore be avoided during breast-feeding. Should smoking withdrawal not be achieved, oral forms of nicotine replacement therapy should be preferred compared with nicotine patches as intermittent dose forms would minimize the amount of nicotine in breast milk and permit feeding when levels were at their lowest. 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. The relatively small amounts of nicotine found in breast milk during NRT use are less hazardous to the infant than second-hand smoke.

Fertility

Smoking increases the risk for infertility in women and men. Both in humans and in animals, it has been shown that nicotine can adversely affect sperm quality. In animals, reduced fertility has been shown.

4.7 Effects on ability to drive and use machines

There is no evidence of any risks associated with driving or operating machinery when Nicotinell TTS is used following the recommended dose. Nevertheless, one should take into consideration that smoking cessation can cause behavioural changes.

4.8 Undesirable effects

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

Clinical trial experience has shown that skin reactions at the application sites are the most frequent adverse reactions. This led to the premature discontinuation of Nicotinell transdermal patch in approximately 6% of clinical trial participants. These reactions include application site burning, oedema, erythema, irritation, pruritus, rash, urticaria and vesicles. 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 (can not to 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*	headache, dizziness	Very Common
	motor dysfunction, tremor	Common
	paraesthesia, dysgeusia and blurred vision	Uncommon
Cardiac disorders	palpitations	Common
	tachycardia	Uncommon
	chest pain** and arrhythmia	Rare
Vascular disorders	hypertension and hot flush	Uncommon
Respiratory, thoracic and mediastinal disorders	cough, pharyngitis, dyspnoea	Common
	upper respiratory tract infections	Uncommon
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
	skin discoloration, cutaneous vasculitis	Rare
	allergic dermatitis *, contact dermatitis*, photosensitivity	Very Rare

Musculoskeletal, connective tissue and bone disorders	myalgia, arthritis	Common
	arthralgia, muscle cramp and back pain	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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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.

Overdose with Nicotinell TTS may occur when many pieces are applied simultaneously on the skin.

Symptoms

Symptoms of acute nicotine poisoning include pallor, hyperhidrosis, tremor, mental confusion, nausea, dyspnoea, cardiac arrhythmia, vomiting, salivation, abdominal pain, diarrhoea, sweating, headache, tachycardia, dizziness, weakness, disturbed hearing and vision. In extreme cases, these symptoms may be followed by hypotension, rapid or weak or irregular pulse, breathing difficulties, prostration, circulatory collapse, coma and terminal convulsions with large overdoses.

Treatment of overdose

Overdose from Topical Exposure

If the patient shows signs of overdose, the patch 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. Artificial respiration with oxygen should be instituted if necessary.

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

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, serotinin, 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 therapy 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 therapy with the patch 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 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 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Absorption

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

Following a single application of the 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 in proportion to the dose of nicotine delivered by the patch. The patch is designed to deliver approximately 0.7mg/cm^2/24 hours

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. Nicotine crosses the blood-brain barrier, placenta, and is detectable in breast milk. The plasma protein binding of nicotine is negligible (< 5%).

Metabolism and 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.

5.2 Pharmacokinetic properties

No additional data.

5.3 Preclinical safety data

Pad
Polyester film
Acrylate esters vinylacetate co-polymers
Fractionated coconut oil
Methacrylic acid esters co-polymers
Aluminised polyester backing film
Aluminised and siliconised polyester film release liner

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Pad
Polyester film
Acrylate esters vinylacetate co-polymers
Fractionated coconut oil
Methacrylic acid esters co-polymers
Aluminised polyester backing film
Aluminised and siliconised polyester film release liner

6.2 Incompatibilities

None known.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Do not store above 25°C

6.5 Nature and contents of container

Heat-seal paper/aluminium/polyamide/polyacrylnitrile pouches (child-resistant) enclosed in a cardboard carton.

or

Heat-sealed paper/ aluminium polyacrylnitrile pouches. Each pouch is enclosed within a child-resistant sachet. Sachets are packed in a cardboard container.

or

Heat-seal Paper / Polyethylene terephthalate/Aluminium/Cyclo olefine copolymer coextrudate pouches (Child -resistant) enclosed in a cardboard carton.

Nicotinell TTS 20 are available in pack sizes of: 2, 3, 7, 14, 21 & 28 patches.

6.6 Special precautions for disposal

Keep all medicines out of the reach of children.

7 MARKETING AUTHORISATION HOLDER

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