

1. NAME OF THE MEDICINAL PRODUCT

Nicotinell TTS[®] 10

Nicotinell TTS[®] 20

Nicotinell TTS[®] 30

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Nicotinell TTS 10 patch contains 17.5 mg S(-)-nicotine which provides an average absorption rate of 7 mg nicotine in 24 hours.

Each Nicotinell TTS 20 patch contains 35.0 mg S(-)-nicotine which provides an average absorption rate of 14 mg nicotine in 24 hours.

Each Nicotinell TTS 30 patch contains 52.5 mg S(-)-nicotine which provides an average absorption rate of 21 mg nicotine in 24 hours.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Transdermal patches

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 10 patch 7mg/24 hour has a drug releasing area of 10 cm² and is printed CG CWC on the patch surface.

Nicotinell TTS 20 patch 14mg/24 hour has a drug releasing area of 20 cm² and is printed CG FEF on the patch surface.

Nicotinell TTS 30 patch 21mg/24 Hour has a drug releasing area of 30 cm² and is printed CG EME on the patch surface.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Aid to smoking cessation

4.2 Posology and method of administration

Adults:

For individuals smoking 20 cigarettes or more a day, it is recommended that treatment be started with Nicotinell TTS 30 (Step 1) once daily, applied to a dry non-hairy area of the skin on the trunk or upper arm. Those smoking less than this are recommended to start with Nicotinell TTS 20 (Step 2). Sizes of

30cm², 20cm² and 10cm² are available to permit gradual withdrawal of nicotine replacement, using treatment periods of 3-4 weeks (for each size). The size 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.

The dosage must not be adjusted by cutting a patch.

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. 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 several days should be allowed to elapse before a new patch is applied to the same area of skin.

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.

Children and young adults:

The above recommendation can be used for adolescences between 12 and 18 years of age. As data are limited in this age group, medical advice should be obtained should it be found necessary to use the patch beyond 12 weeks.

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.

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 nonsmokers 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.

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.

Underlying 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 nonpharmacological 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.

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.

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.

GastroIntestinal-disease

Nicotinell TTS should be used with caution in patients with peptic ulcers.

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

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 slower metabolism and a consequent rise in blood levels of such drugs.

4.5 Interaction with other medicinal products and other forms of interaction

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

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 fetus 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. 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 fetus would not normally be exposed to nicotine.

Breast feeding

The relatively small amounts of nicotine found in breast milk during NRT use are less hazardous to the infant than second-hand smoke. Intermittent dose forms would minimize the amount of nicotine in breast milk and permit feeding when levels were at their lowest.

4.7 Effects on ability 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.

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.

Adverse reactions are listed below by system organ class and frequency. Frequencies are defined as: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$), or not known (can not be estimated from available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

SYSTEM ORGAN CLASS (MedDRA classification)	VERY COMMON ($\geq 1/10$)	COMMON ($\geq 1/100$ to $< 1/10$)	UNCOMMON ($\geq 1/1,000$ to $< 1/100$)	RARE ($\geq 1/10,000$ to $< 1/1,000$)	NOT KNOWN (can not be estimated from available data)
Immune system disorders	-	-	-	-	Allergic reactions such as urticaria, rash and pruritus; angioedema and anaphylactoid reaction
Psychiatric disorders*	-	agitation, anxiety, nervousness, insomnia, abnormal dreams	disturbance in attention, somnolence, affect lability, irritability, depressed mood and confusional state	-	-
Nervous system disorders*	-	headache, dizziness, motor dysfunction	paraesthesia, dysgeusia and blurred vision	tremor	-
Cardiac disorders	-	-	palpitations	chest pain, dyspnea and arrhythmia	-
Vascular disorders	-	-	Hypertension and hot flush	-	-
Respiratory, thoracic and mediastinal disorders	-	cough	Upper respiratory tract infections	-	-
Gastrointestinal disorders*	-	nausea, abdominal pain, dyspepsia	vomiting, constipation, diarrhea, flatulence, dry mouth	-	-
Skin and subcutaneous tissue disorders	-	-	hyperhidrosis	Skin discoloration, cutaneous vasculitis	-
Musculoskeletal, connective tissue and bone disorders	-	myalgia, arthritis	arthralgia, muscle cramp and back pain	-	-
General disorders and	application site reactions	-	asthenic conditions,	-	-

administration site conditions			pain and discomfort		
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*Symptoms may be ascribed also to withdrawal symptoms in connection with smoking cessation and may be due to insufficient replacement of nicotine

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.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form <https://sideeffects.health.gov.il>

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 nonsmoker, would be more toxic, because of the development of tolerance.

The acute lethal dose of nicotine in a nontolerant man has been estimated to be 0.5-0.75 mg per kg body weight, corresponding in an adult to 40 to 60 mg. 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 nausea, vomiting, salivation, abdominal pain, diarrhoea, sweating, headache, tachycardia, dizziness, marked 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.

Management of overdose

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). 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. The patient should then be treated symptomatically. Artificial respiration with oxygen should be instituted if necessary.

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, serotonin, vasopressin, betaendorphin, growth hormone, cortisol and ACTH. These neuroregulators may be involved in the reported behavioral 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.

5.2 Pharmacokinetic 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 12 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/cm²/24 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.

5.3 Preclinical safety data

No additional data.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Acrylates/Vinyl Acetate Copolymer
Siliconized Polyester Film
Eudragit E
Aluminium Coated Polyester Foil
Medium Chain Triglycerides,

6.2 Incompatibilities

None known.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store below 30°C

6.5 Nature and contents of container

Paper/Aluminium/Polyamide/Polyacrylonitrile pouches which consist of the following layers (from outside to inside): Paper, adhesive, aluminium foil, adhesive, polyamide, adhesive, PAN (polyacrylonitrile)

6.6 Special precautions for disposal and other handling

Keep all medicines out of the reach of children.

7. MANUFACTURER

Dr. Reddy's Laboratories SA, Basel, Switzerland

8. MARKETING AUTHORISATION HOLDER

Professional Pharma Ltd., 16 Shenkar Arie st., Herzliya 4672516, Israel

9. MARKETING AUTHORISATION NUMBER(S)

Nicotinell TTS 10: 056-89-26984

Nicotinell TTS 20: 057-22-26983

Nicotinell TTS 30: 056-90-26988

Revised in 03.2026.