Nicotinell® TTS

Transdermal therapeutic system (TTS)
Aid to smoking cessation (on a scientific basis)

Composition

Active substance: nicotine. Transdermal therapeutic system (TTS) with a contact surface of 10 cm^2, 20 cm^2, or 30 cm^2.
1 Nicotinell TTS 10 contains 17.5 mg nicotine. The average rate of active substance release onto the skin is 7 mg/24 hours.
1 Nicotinell TTS 20 contains 35 mg nicotine. The average rate of active substance release onto the skin is 14 mg/24 hours.
1 Nicotinell TTS 30 contains 52.5 mg nicotine. The average rate of active substance release onto the skin is 21 mg/24 hours.

Properties/Effects (therapeutic action)

The main pharmacological effect of nicotine is stimulation of the sympathetic and parasympathetic nervous systems, which brings about cardiovascular effects such as an increase in blood pressure and heart rate, and a cholinergic effect, which stimulates the central nervous system, relaxes skeletal muscle, and raises gastrointestinal motility and secretion.
Depending on the patient's initial clinical status, the effects of nicotine during smoking are experienced as stimulating or relaxing, and can be controlled by the pattern of smoking.
Partial or complete tolerance to some effects of nicotine develops rapidly. Application of Nicotinell TTS (20 cm^2) to smokers abstinent overnight resulted in small increases in mean heart rate (up to 6 beats per minute) and systolic blood pressure and a decrease in stroke volume. The changes in heart rate and stroke volume were still present at day 10 after repeated application, suggesting that development of complete tolerance to the effects of nicotine did not occur. The effects were smaller in magnitude than those produced by cigarette smoking, whereas no changes in skin temperature of blood flow were observed compared with placebo control.
During tobacco withdrawal, symptoms such as craving, irritability, frustration, anger, restlessness, nervous tension, anxiety, feeling of hunger, weight gain, difficulties of concentration, and sleep disturbances have been observed.
During placebo-controlled double-blind clinical studies, nicotine replacement with Nicotinell TTS in the first few weeks or months after stopping smoking increased the chances of successful abstinence with or without psychotherapeutic support. There was also a strong trend towards reduction of withdrawal symptoms.

Pharmacokinetics

Absorption
Nicotine is absorbed rapidly through the skin and mucous membranes, as well as by inhalation, and is distributed widely in the body tissue. In this transdermal therapeutic system nicotine is used in the form of its free base. After applying Nicotinell TTS, nicotine is absorbed continuously through intact skin.

Distribution
The absorption profile after single application of Nicotinell TTS to healthy abstinent smokers (subjects undergoing a course of smoking cessation therapy with the patch) shows an initial 1–2 hours delay followed by a progressive rise in plasma concentrations, plateaus being attained at about 8–10 hours after application. Peak plasma concentrations of 12.3 ng/mL were reached with Nicotinell TTS 30 cm^2.
After the system is removed, plasma concentrations decline more slowly than would be predicted by the 2-hour elimination half-life for this drug after an intravenous infusion. This is because about 10% of the total amount of nicotine that reaches the circulation is delivered from the skin after Nicotinell TTS is removed.
In comparison with an i.v. infusion, 76.8% of the nicotine released from Nicotinell TTS is systemically available. The pharmacokinetic values, in particular the area under the plasma concentration curve, are in linear proportion to the dosage. With repeated application of 20 cm^2 and 30 cm^2 Nicotinell TTS mean minimum and maximum plasma concentrations at steady state were 7.1 ng/mL and 12.0 ng/mL for the 20 cm^2 patch and 10.3 ng/mL and 17.7 ng/mL for the 30 cm^2 patch.
These plasma concentrations were within the range observed during moderate cigarette smoking, e.g. one cigarette an hour.
Nicotine is distributed widely in the body with a volume of distribution of approximately 180 L. It crosses the blood-brain barrier, the placenta, and is also found in breast milk. Plasma protein binding of nicotine is negligible, less than 5%. Total plasma clearance of nicotine ranges from 0.92 to 2.43 L/min.

Metabolism
Nicotine is eliminated mainly via hepatic metabolism, and the primary metabolites are cotinine and nicotine-1'-N-oxide. Neither of the principal metabolites is considered to be pharmacologically active.

Elimination
The elimination half-life of nicotine is about 2 hours, and plasma clearance is between 0.92 and 2.43 L/min.
Only small amounts of nicotine are eliminated in unchanged form via the kidneys.
Renal excretion of unchanged nicotine represents 5–10% of total excretion and is pH-dependent, being negligible under alkaline conditions. Cumulation is only slight.

Indications/Methods of use

To aid smoking cessation; to reduce addictive behaviour and the various withdrawal symptoms in nicotine-dependent smokers.
Treatment should not exceed 3 months. Data currently available show that application of Nicotinell TTS compared with placebo is effective in the short term. The long-term success of treatment after smoking cessation does not depend on Nicotinell TTS, but is essentially determined by the patient's willpower and any further psychological support he or she may be receiving.

Dosage/Directions for use

The patient should be told to stop smoking completely as soon as treatment with Nicotinell TTS is started.
Nicotinell TTS is intended for use in adults over the age of 18 years.
One Nicotinell TTS should be applied daily and left on the skin for 24 hours. Since the amount of nicotine released from Nicotinell TTS per cm^2 is constant, the dose administered is determined solely by the contact area of the system. To avoid local irritation of the skin, a new site of application should be chosen each day. Nicotinell TTS is available in three dosage strengths: Nicotinell TTS 30, Nicotinell TTS 20, and Nicotinell TTS 10. The dosage cannot be adjusted by cutting the TTS transdermic system.
Nicotinell TTS 30 is generally intended for smokers with a consumption of more than 20 cigarettes a day. Nicotinell TTS 20 is sufficient for smokers with a consumption of up to 20 cigarettes daily. Nicotinell TTS 10 is designed to reduce nicotine replacement towards the end of therapy.
Treatment should be initiated with one of the larger systems (Nicotinell TTS 30 or 20) and reduced in stages. The dosage can be adapted to the patient's response after a few days.
Heavy smokers shoud be given Nicotinell TTS 30 followed by Nicotinell TTS 20 and finally Nicotinell TTS 10 for about 4 weeks in each case.
Moderate smokers should use Nicotinell TTS 20 for about 8 weeks and Nicotinell TTS 10 for about 4 weeks.
Smoking cessation therapy should not expose the user to more nicotine than smoking.
After removing the protective foil, the nicotine patch should be applied to a clean, dry, and intact area of skin (free from lotion, alcohol, or traces of ointment), preferably on the trunk, or otherwise on the upper arm or hip, and pressed on with the palm of the hand for 10 seconds. A different site of application should be chosen each day.
In the patient has not stopped smoking with the aid of Nicotinell TTS at the end of the treatment period, treatment should be discontinued.
Another withdrawal attempt can be made with Nicotinell TTS at a later point.

Note
Nicotinell TTS can be used to supplement smoking cessation programmes, self-motivation techniques, behavioural therapy, or psychotherapy.

Restrictions on use

Contraindications
Hypersensitivity of the skin to nicotine or one of the components of TTS; systemic skin diseases; unstable or worsening angina pectoris; acute myo-cardial infarction; severe cardiac arrhythmias; *recent cerebrovascular accident;* pregnancy and lactation.

Precautions
The patient should be urged to stop smoking completely when using Nicotinell TTS. Patients 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.
Given the pharmacological effects of nicotine, the use of Nicotinell TTS calls for careful weighing of the risks and benefits before it can be considered in patients with the following diseases:
– stable angina pectoris
– status postmyocardial infarction
– occlusive peripheral arterial diseases
– cerebrovascular diseases
– arrhythmias
– heart failure
– disturbance of renal or hepatic function
– diabetes mellitus
– hypertension
– hyperthyroidism
– peptic ulcer
Allergic reactions: in clinical studies, contact sensitivity occurred in a few patients when using transdermal nicotine. In such cases, it should be noted that contact sensitivity may recur when other nicotine-containing products, including tobacco, are used.
Intermittent use: There is no sufficient data on the intermittent use of Nicotinell TTS. However, in case of chronic insomnia, the patch can be removed after 16 hours.

Pregnancy, breast feeding
No controlled studies in pregnant women are available. Nicotinell TTS should not be used during pregnancy and breast feeding. Nicotine passes into the breast milk.

Undesirable side effects

In principle, Nicotinell TTS can cause nicotine side effects similar to those associated with smoking. However, smoking carries additional risks because of the known harmful effects of carbon monoxide, irritant gases, and tar. Since the plasma nicotine concentrations produced by Nicotinell TTS are substantially lower than those produced by smoking, the nicotine side effects during treatment with Nicotinell TTS can be expected to be less marked. However, if the patient continues to smoke while using Nicotinell TTS, the side effects of nicotine may be more frequent and more pronounced.
The following adverse events/withdrawal symptoms were reported in three double-blind clinical trials, irrespective of causal association with Nicotinell TTS (frequency at least 0.5% greater than with placebo):

Skin
Owing to the properties of the active substance, nicotine, Nicotinell TTS may cause mild erythema and pruritus in up to 35% of patients. The incidence of severe erythema, which can be reversed by removing the system, increases from the third week of treatment (up to 8% of cases). Allergy, herpes, and rash have been observed in rare cases.
Nicotinell TTS is left on the skin for one day, producing an occlusive effect. This effect can cause skin irritation in the form of dermatitis. As with normal adhesive plasters, reactions may occur as a result of intolerance to the adhesive.
Eryhema usually disappears within a few hours of removing the system. To reduce local irritation a different site of application should be chosen each day. Patients with a known history of allergy to adhesive plasters should be carefully monitored for skin reactions during the first few days of treatment.

Central nervous system
Headache (in about 30% of patients), frequently dizziness, nausea, and sleep disturbances.
Rare: impaired concentration, abnormal dreaming, fatigue, dry mouth, confusion, migraine, increased sweating, increased appetite.

Cardiovascular system
Rare: increase in heart rate and blood pressure changes.
If the cardiovascular system is already compromised, symptoms of coronary heart disease (e.g. angina pectoris) and/or peripheral arterial occlusive disease (intermittent claudication) could be exacerbated.

Gastrointestinal tract
Rare: abdominal pain, dyspepsia, vomiting, peptic ulcer, flatulence, dysphagia.

Other organ systems
Frequent: influenza-like symptoms.
Rare: motor dysfunction, chest pain.
Isolated cases of urticaria, angioneurotic oedema, and dyspnoea have been reported.

Interactions

The enzyme induction observed in smokers is not attributable to nicotine, but to the tar compounds contained in tobacco smoke. This means that when tobacco consumption ceases, even if nicotine is replaced with Nicotinell TTS, there may be a change (normalisation) in the metabolism and the pharmacological effects of concomitant medication. Smoking can lower serum concentrations of some drugs, such as phenazone, estrogens, nordazepam, lidocaine, oxazepam, warfarin, phenacetin, caffeine, theophylline, imipramine, and pentazocine. Other reported effects of smoking include reduced analgesic efficacy of propoxyphene, reduced diuretic response to furosemide, and altered pharmacological response to propranolol, as well as altered rates of ulcer healing with H_2-antagonists.
Both smoking and nicotine can increase levels of circulating cortisol and catecholamines. Dosages of nifedipine, adrenergic agonists, or adrenergic blocking agents may need to be adjusted.
Smoking cessation, even under (partial) nicotine substitution with Nicotinell TTS, may eliminate the above-mentioned phenomena. Therefore, in patients who are being treated with the above-mentioned drugs while undergoing smoking cessation, it may be necessary to adapt the dosage of the co-medication. Owing to the various pharmacological effects of nicotine on the sympathetic and parasympathetic nervous systems, the action of beta-blockers may be influenced in various ways.

Overdosage

Toxic effects
The toxicity of nicotine cannot be directly compared to that of smoking, because tobacco smoke contains additional toxic substances (e.g. carbon monoxide, irritant gases, and tar).
Chronic smokers can endure doses of nicotine that would be more toxic in a non-smoker, owing to the development of tolerance.
Application of several Nicotinell TTS patches could result in serious overdosage. Slower absorption after cutaneous exposure to nicotine favour 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.

Acute effects
The acute fatal dose of nicotine in adults is 40–60 mg nicotine orally. This is equal to the amount of nicotine in 4–6 cigarettes or in one cigar. In children, the following symptoms have been described after ingestion of tobacco products: vomiting, agitation, nausea, diarrhoea, pallor, weakness, absence of reactions, and twitching of the extremities.

Acute toxic effects
Signs and symptoms of overdosage would be the same as those of acute nicotine poisoning. In non-smokers, these include pallor, sweating, nausea, salivation, vomiting, abdominal cramps, diarrhoea, headache, dizziness, hearing and vision disturbances, tremor, mental confusion, muscle weakness, convulsions, prostration, absence of neurological reactions, 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.

Chronic effects
The development of tachyphylaxis is a feature of chronic smoking, which means that chronic smokers can tolerate acute, highly toxic doses of nicotine. Chronic overdosage may produce symptoms similar to those characteristic of acute nicotine poisoning.

Management
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). 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.
Other treatment measures for acute nicotine poisoning include artificial respiration in the case of respiratory paralysis, maintaining normal body temperature, and treatment for hypotension and cardiovascular collapse.

Further remarks

Incompatibilities
Local tolerability of Nicotinell TTS: In transdermal drug administration a distinction should be made between skin tolerability of the active substance (in this case nicotine) and that of the system itself.

Safety note concerning children
Nicotine is a highly toxic substance. Even the dose tolerated by adults during treatment can produce severe symptoms of poisoning in small children. In other words, application of Nicotinell TTS in play can be fatal for children if not noticed in time. Nicotinell TTS must therefore be kept out of the reach of children at all times.
To protect children, Nicotinell TTS is sealed in a child-resistant sachet. This sachet should be opened immediately before use with a pair of scissors, taking care that the patch inside is not damaged.
The patches still contain nicotine after use and must be disposed of so that they do not fall into children's hands.

Storage
Do not store above 30 °C.
The product may be used up to the date ‹EXP› shown on the pack.

Packaging

Nicotinell TTS 10: 7 and 28 systems.
Nicotinell TTS 20: 7 and 28 systems.
Nicotinell TTS 30: 7 and 28 systems.
For further pack sizes, see country-specific information.

Novartis Consumer Health SA Nyon Switzerland

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NOVARTIS

(THIS IS A MEDICAMENT)

– Medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
– Follow strictly the doctor's prescription, the method of use, and the instructions of the pharmacist who sold the medicament.
– The doctor and the pharmacist are experts in medicine, its benefits and risks.
– Do not by yourself interrupt the period of treatment prescribed for you.
– Do not repeat the same prescription without consulting your doctor.

Keep medicament out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists