PRODUCT MONOGRAPH

Pr NICORETTE® INVISIPATCH™

Nicotine Transdermal System
25 mg nicotine/ 16 hours

Mfr. Std.

Stop Smoking Aid

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Nicotine Transdermal System
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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Table 1

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
transdermal	**Pr NICORETTE® INVISIPATCH™** 25 mg nicotine/ 16 hours	**Pr NICORETTE® INVISIPATCH** • acrylic adhesive containing Durotak 387-2051, • Butylated methacrylate copolymer and medium-chain triglycerides, • polyethylene terephthalate • croscarmellose sodium • aluminum acetylacetonate

INDICATIONS AND CLINICAL USE

Patch-Alone Treatment
NICORETTE INVISIPATCH (Nicotine Transdermal System), applied while patients are awake, is indicated as a temporary aid to facilitate smoking cessation in smokers with a strong desire to quit and to provide partial substitution for the nicotine in cigarettes in order to lessen withdrawal symptoms of smoking cessation. NICORETTE INVISIPATCH treatment should be used as part of a comprehensive behavioral smoking-cessation program.

Strengths of nicotine patches available in the NICORETTE transdermal system are: 5, 10, 15 and 25 mg / 16 hr.

The highest dose (25 mg) is available as a prescription medication, while the other doses are natural health products subject to the Natural Health Products Regulations and are not prescription drugs

Combination Patch plus Gum (only for patches up to 15 mg)
The NICORETTE INVISIPATCH, when used up to the strength of 15 mg per patch, may be used alone

or in combination with NICORETTE 2 mg gum. Combination treatment may be helpful for some patients who have relapsed with the patch in the past, or in cases of breakthrough cravings or difficulties controlling cravings while on the patch alone.

Geriatrics (> 60 years of age):
The initial dose in elderly patients may have to be adjusted because their concomitant conditions, including hepatic impairment, may increase risk. **(See WARNINGS AND PRECAUTIONS and ACTION AND CLINICAL PHARMACOLOGY).** Seventy-nine patients over the age of 60 participated in clinical trials of NICORETTE therapy. Based on this limited evidence from clinical trials, NICORETTE therapy appeared to be as effective in this age group as in younger smokers. NICORETTE therapy appeared to be as effective in this age group as in younger smokers.

Pediatrics (< 18 years of age): NICORETTE INVISIPATCH is contraindicated in persons under 18 years of age. (See **WARNINGS AND PRECAUTIONS**).

CONTRAINDICATIONS

- Patients who are hypersensitive to nicotine or to any ingredient in the formulation or component of the transdermal system. (For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.)
- Patients with generalized skin disorders;
- Never smokers or occasional smokers;
- Persons under 18 years of age **(See WARNINGS AND PRECAUTIONS)**
- Pregnant women or nursing mothers **(See WARNINGS AND PRECAUTIONS**); and
- Patients during the immediate post-myocardial infarction period, patients with life-threatening arrhythmias, patients with severe or worsening angina pectoris and patients who have had a recent cerebral vascular accident **(See WARNINGS AND PRECAUTIONS**).

WARNINGS AND PRECAUTIONS

General
Nicotine from any source can be toxic and addictive. For any smoker, with or without concomitant disease, the risk of nicotine replacement in a smoking cessation program should be weighed against the hazard of continued smoking.

The patient should stop smoking completely when initiating NICORETTE INVISIPATCH therapy (Nicotine Transdermal System) **(See DOSAGE AND ADMINISTRATION**). Patients should be informed that they should not continue to smoke while using NICORETTE INVISIPATCH, because they may experience adverse effects due to peak nicotine levels higher than those experienced from smoking alone.

If there is a clinically significant increase in cardiovascular or other effects attributable to nicotine, the NICORETTE INVISIPATCH dose should be reduced or the treatment discontinued.

The use of NICORETTE INVISIPATCH system beyond 12 weeks by patients who stop smoking should be discouraged because the chronic consumption of nicotine by any route can be harmful and addicting. If the patient continues to smoke, treatment should be discontinued.

Safety Note Concerning Children and Pets:

The NICORETTE INVISIPATCH (Nicotine Transdermal System) can cause severe poisoning or even prove fatal if applied or ingested by children or pets. Used patches contain approximately 40% of their initial nicotine content. Therefore, patients should be cautioned to keep both the used and unused NICORETTE INVISIPATCH patches out of the reach of children and pets.

Circumstances when NICORETTE INVISIPATCH should be removed

Risk of Unintentional Increase in Nicotine Exposure

Strenuous exercise*:* Preliminary evidence suggests that wearing a nicotine transdermal patch during periods of strenuous exercise may lead to nicotine toxicity as a result of increased absorption of nicotine from the depot of nicotine in the skin under the patch, due to increased skin temperature and increased cutaneous vasodilation and perfusion from exercising. Three cases illustrating this phenomenon were described in Health Canada Adverse Reaction Newsletter, Volume 6, Number 1, January, 1996. Advice to remove the nicotine patch before engaging in strenuous exercise was recommended by; W. Dafoe and P. Huston, Current Trends in Cardiac Rehabilitation, Canadian Medical Association Journal, February 15, 1997; 156(4) 527-532. Until definitive studies have been undertaken to clarify this hazard, it is advisable to remove the nicotine patch prior to engaging in strenuous activity.

Prolonged exposure to heat, including fever: Similarly, due to likelihood of increased skin temperature and perfusion, all patients should be advised to remove the patch prior to exposure of saunas and hot whirlpool spa baths, intensive sunbathing, heating pads, electric blankets, heated water beds, heat lamps, hot water bottles. As well, patients with fever should be monitored for nicotine side effects.

Risks of Burns from MRI procedure: NICORETTE INVISIPATCH should be removed prior to undergoing any Magnetic Resonance Imaging (MRI) procedures to prevent the risk of burns.

Concomitant use with CHAMPIX (varenicline)
The concomitant use of nicotine replacement therapy (NRT) with CHAMPIX (varenicline tartrate), a non-nicotine prescription smoking cessation drug, may result an increase, over NRT alone, in the likelihood of experiencing the more common adverse events, such as nausea, headache, vomiting, stomach upset, or fatigue. Due to the mechanism of action of varenicline, the combination is not expected to improve the likelihood of successfully quitting smoking. The safety and efficacy of the combination treatment with CHAMPIX and NRT have not been studied.

Cardiovascular
The risks of nicotine replacement in patients with certain cardiovascular and peripheral vascular diseases should be weighed against the benefits of including nicotine replacement in a smoking-cessation program for them. Specifically, patients with coronary heart disease (history of myocardial infarction and/or angina pectoris), serious cardiac arrhythmias, or vasospastic diseases (Buerger's disease, Prinzmetal's variant angina) should be carefully screened and evaluated before nicotine replacement is recommended.

Palpitations occurring in association with the use of NICORETTE INVISIPATCH therapy have been reported occasionally. If serious cardiovascular symptoms occur with the use of NICORETTE INVISIPATCH therapy, should be discontinued.

Dependence/Tolerance

NICORETTE INVISIPATCH therapy is generally considered to have a low dependency potential as compared to cigarettes, based on differences between it and cigarettes in four characteristics commonly considered important in contributing to dependency: much slower absorption, much smaller fluctuations in blood levels, lower blood levels of nicotine, and less frequent use (i.e., once daily). Transferred nicotine dependency from cigarettes to nicotine replacement therapies may occur but is rare.

To minimize the risk of dependence, therapy should not exceed 12 weeks **(See DOSAGE AND ADMINISTRATION**).

Endocrine and Metabolism

NICORETTE INVISIPATCH therapy should be used with caution in patients with hyperthyroidism pheochromocytoma, or insulin-dependent diabetes since nicotine causes the release of catecholamines by the adrenal medulla.

Gastrointestinal

Nicotine delays healing in peptic ulcer disease; therefore, NICORETTE INVISIPATCH therapy should be used with caution in patients with active peptic ulcers and only when the benefits of including nicotine replacement in a smoking-cessation program are considered to outweigh the risks.

Hepatic/Biliary/Pancreatic

The pharmacokinetics of nicotine have not been studied in patients with hepatic impairment; however, given that nicotine is extensively metabolized and that its total system clearance is dependent on liver blood flow, some influence of hepatic impairment on drug kinetics (reduced clearance) should be anticipated.

Renal

The pharmacokinetics of nicotine have not been studied in patients with renal impairment; however, given that nicotine is extensively metabolized and that its total system clearance is dependent on liver blood flow, some influence of hepatic impairment on drug kinetics (reduced clearance) should be anticipated. Only severe renal impairment would be expected to affect the clearance of nicotine or its metabolites from the circulation.

Sensitivity/Resistance

Patients with acute hypersensitivity reactions should discontinue use of NICORETTE INVISIPATCH and should be advised of the possibility of acute hypersensitivity reactions to other forms of nicotine, including cigarettes.

Skin

NICORETTE INVISIPATCH systems are usually well tolerated by patients with normal skin, but may be irritating for patients with some skin disorders (atopic or eczematous dermatitis).

Patients should be instructed to discontinue promptly the use of NICORETTE INVISIPATCH system and contact their physician if they experience severe or persistent local skin reactions (e.g. urticaria, hives, or generalized rash). Patients using NICORETTE INVISIPATCH therapy concurrently with other transdermal systems may exhibit local reactions at both application sites. In such patients use of one or both systems may have to be discontinued. Serious allergic reactions may occur rarely. About

1% of patients dropped out of clinical trials due to skin reactions; none had classical contact sensitization.

Special Populations

Pregnant Women:

Pregnant smokers should be encouraged to attempt cessation using educational and behavioral interventions before using pharmacological approaches.

Tobacco smoke (containing nicotine, hydrogen cyanide and carbon monoxide) has been shown to be harmful to the fetus. Nicotine has been shown in animal studies to cause fetal harm. There is a possibility that nicotine from NICORETTE INVISIPATCH system can cause fetal harm when administered to a pregnant woman. Women of child-bearing potential should be advised to take adequate precautions to avoid becoming pregnant while using NICORETTE INVISIPATCH (see **CONTRAINDICATIONS**).

Nursing Women:

The safety of NICORETTE INVISIPATCH therapy in nursing infants has not been examined. Nicotine passes freely into breast milk; the milk to plasma ratio averages 2.9. Nicotine is absorbed orally (see CONTRAINDICATIONS).

Pediatrics (< 18 years of age):

NICORETTE INVISIPATCH is not to be used by persons under 18 years of age. The use of NICORETTE INVISIPATCH in children and adolescents who smoke has not been evaluated (see **CONTRAINDICATIONS**).

Geriatrics (> 60 years of age):

The pharmacokinetics of nicotine have not been studied in the elderly; however, given that nicotine is extensively metabolized and that its total system clearance is dependent on liver blood flow, some influence of hepatic impairment on drug kinetics (reduced clearance) should be anticipated. Only severe renal impairment would be expected to affect the clearance of nicotine or its metabolites from the circulation.

Seventy-nine patients over the age of 60 participated in clinical trials of NICORETTE therapy. The initial dose in elderly patients may have to be adjusted because their concomitant diseases, including hepatic impairment, may increase risk.

Monitoring and Laboratory Tests

No specific monitoring or laboratory tests are required while using NICORETTE INVISIPATCH.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Assessment of adverse events in patients who participated in controlled clinical trials is complicated by the occurrence of GI and CNS effects of nicotine withdrawal as well as nicotine excess. The actual incidences of both effects are confounded by concurrent smoking by many of the patients. When reporting adverse events in the clinical trials, the clinical investigators did not attempt to identify the cause of the symptom

The most common adverse event associated with NICORETTE system is a mild, short-lived erythema and/or pruritus at the application site. Erythema and/or pruritis were seen at least once in 47% of patients on the NICORETTE system (versus 45% of patients on placebo) in the clinical efficacy trials. These signs were not considered clinically relevant and usually disappeared within one hour. After removal of the system, local erythema was noted at least once in 7% of patients and local edema in 3% of patients.

Erythema generally resolved within 24 hours. About 1% of patients dropped out of the clinical trials due to skin reactions. None of these were classified as contact sensitization reactions.

In the prescription to OTC switch trials approximately 32% of reported events were skin reactions.

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

General

NICORETTE system 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.
Some symptoms, such as dizziness, headache and sleeplessness may be related to withdrawal symptoms associated with abstinence from smoking. Increased frequency of aphthous ulcer may occur after abstinence from smoking. The causality is unclear.

Patch-Only Trials

25 mg patch (CEASE trial)

The CEASE study involved subjects who smoked at least 15 cigarettes per day, with study endpoint at 12 months (see CLINICAL TRIALS for details). Table 2 summarizes those adverse events that occurred in the first 8 weeks of the study, at an incidence of greater than 1% in the following two arms: 15 mg patch for 8 weeks treatment and 25 mg patch for 8 weeks treatment.

Table 2: NICORETTE treatment-emergent adverse events that occurred in >1% of subjects in either of the two drug treatment arms, and greater than in the placebo arm, during Weeks 1 - 8 of the CEASE study. Each event reported once per subject

Body System	Preferred Term	Nicorette 25 mg (8 weeks tmt) n= 715 %	Nicorette 15 mg (8 weeks tmt) n= 716 %	Placebo n= 714 %
Skin & Appendages Disorders	PRURITUS	17	13	6
	RASH ERYTHEMATOUS	5	4	3
	RASH	1	1	1
Musculo-Skeletal System Disorders	HEADACHE	6	6	4
	INSOMNIA	5	6	6
	SOMNOLENCE	2	1	1
	PARAESTHESIA	2	2	1
	MYALGIA	1	2	1
Gastro-Intestinal System Disorders	NAUSEA / VOMITING	7	5	4
	CONSTIPATION	2	1	2
	DYSPEPSIA	2	2	2
	ABDOMINAL PAIN	1	1	1
	MOUTH DRY	1	1	1
Heart Rate & Rhythm Disorders	TACHYCARDIA	2	2	0
	PALPITATION	1	2	1
Respiratory System Disorders	COUGHING	1	1	0
	RHINITIS	1	0	0

The AEs experienced in the CEASE study were generally similar in nature and severity to the known safety profile for the NICORETTE. Pruritis, as well as nausea and/or vomiting were the only AEs that appeared to be more frequent in the NICORETTE 25 mg dose compared with the NICORETTE 15 mg dose.

Less Common Clinical Trial Adverse Drug Reactions (<1%) reported in the CEASE trial

Skin & Appendages Disorders: acne, alopecia, dermatitis, dermatitis exfoliative, eczema, erythema multiform, erythema nodosum, photosensitivity reaction, application site reaction, pruritus

genital, rash follicular, rash maculo-papular, seborrhea, skin discoloration, skin disorder, urticaria, urticaria acute, dermatitis contact, bullous eruption, skin nodule, erythema induratum, skin cold clammy, pigmentation agnormal, skin dry, skin exfoliation, folliculitis, psoriasis
Musculo-Skeletal System Disorders: Arthralgia, arthrosis, tendonitis, skeletal pain, sciatica, fracture
Central & Peripheral Nervous System Disorders: ataxia, dizziness, dysphonia, hyperesthesia, hyperkinesia, hypertonia, hypoesthesia, neuralgia, stupor, tremor, vertigo, withdrawal headache, cramps legs, migraine aggravated
Vision Disorders: conjunctivitis, vision abnormal, circulatory disorder, conjunctival disorder, irritation eye
Hearing & Vestibular Disorders: tinnitus, ear disorder NOS, parosmia, taste loss, taste perversion, taste comments
Psychiatric Disorders: confusion, aggressive reaction, agitation, amnesia, anorexia, anxiety, apathy, appetite increased, depersonalization, depression psychotic, emotional lability, euphoria, hallucination, libido decreased, libido increased, paranoia, personality disorder, sleep disorder, thinking abnormal, yawning, concentration impaired, dreaming abnormal, sleep increased
Gastro-Intestinal System Disorders: diarrhea, saliva increased, tenesmus, duodenal ulcer, duodenal ulcer hemorrhagia, dyspepsia, dysphagia, eructation, flatulence, gastric dilatation, gastritis, gastroenteritis, glossitis, gum hyperplasia, hematemesis, oral hemorrhage, stomatitis, stomatitus ulcerative, tongue ulceration, hypochlorhydria, gingivitis, diarrhea clostridium difficile, gastro-intestinal disorder NOS, increased peristalsis, hernia NOS, surgical intervention, accident, fistel in the mouth, pain moth, throat irritation
Liver & Biliary System Disorders: biliary pain
Metabolic & Nutritional Disorders: edema generalized, weight increase, edema legs
Cardiovascular Disorders: hypertension, hypotension, edema dependent, ECG agnormal specific, angina pectoris
Myo, Endo, Pericardial & Valve Disorders: angina pectoris
Heart Rate & Rhythm Disorders: bradycardia, arrythmmia, extrasystoles
Vascular (Extracardiac) Disorders: flushing vasodilatation, peripheral ischemia
Respiratory System Disorders: apnea, coughing, dyspnea, hemoptysis, laryngismus, pharyngitis, pleurisy, pneumothorax, rhinitis, sinusitis, sputum increased, upper respiratory tract infection, bronchitis, adult respiratory distress syndrome
Platelet Bleeding & Clotting Disorders: hemorrahge NOS, purpura, epistaxis, gingival bleeding
Urinary System Disorder: cystitis, hematuria, micturition disorder, micturition frequency, polyuria, renal pain, urinary tract infection, urine abnormal
Reproductive Disorders, Male: prostatic disorder
Reproductive Disorders, Female: menstrual disorders, menopausal syndrome, vaginal discomfort
Body as a Whole – General Disorders: withdrawal syndrome, syncope, edema, edema peripheral, allergic reaction, asthenia, back pain, chest pain, chest pain substernal, fever, hot flushes, malaise, pain, infection site pain, rigors, serum sickness, alcohol intolerance, therapeutic response increased, allergy aggravated, allergy, influenza-lide symptoms, leg pain, yellow coloration of body fluid
Resistance Mechanism Disorders: infection, otitis media, herpes zoster, herpes simplex, abscess
Secondary Terms – Events: family stress

<u>15 mg Patches:</u>
Table 3: summarizes the adverse events with an incidence of greater than 1% in 2 placebo-controlled clinical trials and two prescription to OTC switch trials. Duration of the trials range from 12 months to 24 months.

Table 3 Adverse Reactions reported (%) with an Incidence of >1% in Placebo-Controlled Clinical Trials and Prescription to OTC Switch Trials			
Body System/Adverse Event	**Prescription Treatment Groups**		**Prescription to OTC Switch**
	NICORETTE® (n=258)	**Placebo (n=251)**	**NICORETTE (n=3885)**
CNS			
Headache	5.4	4.0	3.3
Vertigo	3.1	0.8	-
Digestive			
Nausea	3.5	4.0	2.4
Flatulence	2.7	2.4	-
Diarrhea	1.9	1.6	-
Taste Perversion	1.9	1.6	-
Mouth Ulceration	1.6	0.4	-
Heartburn/Indigestion	1.2	2.4	-
Tongue Disorder	1.2	0.4	-
Musculoskeletal			
Myalgia	3.1	3.1	-
Skin (Not Application Site)			
Rash/Pruritus/Tingling/Edema	1.9	1.2	-
Acne	1.2	0.0	-
Body as a whole			
Pain	-	-	2.1

In the Kornizter study, in Table 4 (combination nicotine replacement therapy patch + gum) versus patch alone versus placebo), the incidence of local reactions was higher in both the groups that used NICORETTE® Patch than in the placebo group. However, there was no significant difference between the patch + gum and patch alone groups. The incidence of local oral effects was: stomatitis 6.7% (Combination), 10% (patch alone) and 2.7% (placebo); throat irritation 6.7%, 5.3% and 2.7%, respectively and hiccup 7.4%, 0.7% and 0%, respectively. The incidence of local skin reactions after one week of treatment was: erythema 10.1%, 10.1% and 8%, respectively, and itching 10.7%, 10.7% and 1.3%, respectively. The frequency of AEs was highest in the first week, reflecting the higher compliance to treatment at the beginning of the study. The incidence of moderate (which were in a majority) or severe systemic AEs was 20.1%, 20% and 18.7% in the combination group, patch alone group and placebo, respectively during the course of the study. However, there were few withdrawals due to AEs.

In the Puska study, in Table 4 (combination patch + gum versus gum alone) a total of 138/150 (92%) of subjects in the patch + gum group and 136/150 (90.61%) in the gum alone group reported one or more AE. These were mild in the majority of cases (60% in the patch + gum group and 53.3% in gum alone group). The only difference between patch + gum and single gum alone was the incidence of itching (30.7% versus11.3%, respectively). Erythema was reported by 6.7 and 7.3% of subjects in both groups respectively.

The frequency of local oral AEs did not differ significantly between the combination patch + gum group than single gum alone group: sore throat 1.3% and 4%, respectively, sore mouth 3.3% and 4.7%, respectively and throat irritation 0% and 2%, respectively and stomatitis 2.7 and 2.7 respectively. The majority of AEs were mild in intensity.

In the pharmacokinetic study (Study 980-CHC-9134-001), there were no serious AEs or withdrawals due to AEs. There were no unexpected findings. In the clinical pharmacology study (Study T91NT09 [Fagerström et al 1993]), there were no withdrawals due to AEs. No other safety data are presented in the publication.

The data from these studies suggest that safety risk is similar in the group that receive combination patch + gum therapy to that noted in the group receiving single therapy with either patch alone or gum alone. Although ex-smokers using the combination of the patch and the gum may develop both groups of AEs that are formulation specific i.e. application site reactions for the patch and gastro-intestinal events for the gum, the data from these studies do not suggest that this is a problem in clinical usage. The majority of AEs are mild and few patients discontinue usage due to AEs.

Patch + Gum Combination Treatment Trials

Table 4: Summarizes the adverse events with an incidence of greater than 1% in 2 patch + gum combination treatment trials

Table 4: Adverse Event Incidence for Combination Treatment with NICORETTE® 15 mg/16 h Patch plus NICORETTE® 2 mg gum in Clinical Trials Performed in the Belgium and Finland		
	Belgium Trial (Kornitzer) n/N (%)	**Finland Trial (Puska) n/N (%)**
CNS		
Insomnia	2/149 (1.3)	10/150 (6.6)
Dizziness/light-headedness	8/149 (5.3)	-
Vertigo	5/149 (3.3)	2/150 (1.3)
Irritable/fussy	-	-
Headache	9/149 (6.0)	5/150 (3.3)
Gastrointestinal		
Non-specific GI distress	-	-
Indigestion=dyspepsia/constipation	23/149 (15.4)	3/150 (2)
Flatulence	-	2/150 (1.3)
Nausea/vomiting	4/149 (2.6)	2/150 (1.3)
Diarrhea	5/149 (3.3)	-
Gastritis	2/149 (1.3)	-
Local		
Pruritus/itching	16/147 (10.9) (first week)	46/150 (30.7)
Erythema /rash	15/147 (10.2) (first week)	10/150 (6.7)
Stomatitis	10/149 (6.7)	4/150 (0.6)
Throat irritation	10/149 (6.7)	-
Hiccups	11/149 (7.3)	-

Post-Market Adverse Drug Reactions

In addition to the reported effects in clinical trials, the following events have been reported:

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), including isolated reports

Nervous system disorders: Common: Dizziness, headache

Cardiac disorders: Uncommon: Palpitations; Very rare: Paroxysmal atrial fibrillation

Gastrointestinal disorders: Common: Gastro-intestinal discomfort, nausea, vomiting

Skin and subcutaneous tissue disorders: Uncommon: Urticaria

General disorders and administration site conditions: Very common: Itching; Common: Erythema

Reports of Myocardial infarction, cardiac arrest and cerebral hemorrhage including death have been received and a relationship to drug therapy as a contributing factor cannot be excluded.

Rare reports of miscarriage and fetal abnormalities have been received and a relationship to drug therapy as a contributing factor cannot be excluded.

DRUG INTERACTIONS

Overview

Physicians should anticipate that the pharmacokinetics of certain concomitant medications may be altered by smoking cessation with or without nicotine replacement. Therefore the dosage of certain concomitant medications may require adjustment at cessation of smoking. Refer to Table 5.

Drug-Drug Interactions

CHAMPIX (varenicline)

The concomitant use of nicotine replacement therapy with CHAMPIX (varenicline tartrate), a non-nicotine prescription smoking cessation drug, may result an increase, over NRT alone, in the likelihood of experiencing the more common adverse events, such as nausea, headache, vomiting, stomach upset, or fatigue. Due to the mechanism of action of varenicline, the combination is not expected to improve the likelihood of successfully quitting smoking. The safety and efficacy of the combination treatment with CHAMPIX and NRT have not been studied.

Drug-Smoking Cessation Interactions

Table 5 : Established or Potential Drug-Smoking Cessation Interactions

Proper name of drug	Ref	Effect	Clinical comment
Acetaminophen, caffeine, imipramine, oxazepam, pentazocine, propranolol, theophylline	T	Deinduction of hepatic enzymes on smoking cessation	May Require a DECREASE in Dose at Cessation of Smoking
Insulin	T	Increase in subcutaneous insulin absorption with smoking cessation	May Require a DECREASE in Dose at Cessation of Smoking
Adrenergic antagonists (e.g. prazosin, labetalol)	T	Decrease in circulating catecholamines with smoking cessation	May Require a DECREASE in Dose at Cessation of Smoking
Adrenergic agonists (e.g. isoproterenol, phenylephrine)	T	Decrease in circulating catecholamines with smoking cessation	May Require an INCREASE in Dose at Cessation of Smoking

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions
NICORETTE INVISIPATCH should be removed prior to undergoing any Magnetic Resonance Imaging (MRI) procedures to prevent the risk of burns.
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DOSAGE AND ADMINISTRATION

Dosing Considerations

- Patients must desire to stop smoking and should be instructed to stop smoking immediately as they begin using NICORETTE INVISIPATCH (Nicotine Transdermal System) therapy.

- If the patient is unable to avoid cigarette smoking within 2 weeks of starting treatment, NICORETTE therapy should be stopped, since few additional patients in clinical trials were able to quit after this time. The duration of treatment should not exceed 12 weeks.

- The patient should be told to read the consumer information leaflet (**see PART III: CONSUMER INFORMATION**) on NICORETTE INVISIPATCH therapy and should be encouraged to ask questions.

- Smoking cessation should be accompanied by a behavioral support program.

- In all patients, the need for dosage adjustment should be assessed during the first two weeks of therapy.

Recommended Dose and Dosage Adjustment

For those who smoke ≥ 15 cigarettes per day:

- Use one 25 mg patch daily for up to 8 weeks, with gradual weaning subsequently, as per Table 6

Table 6: Recommended Dose Regimen for ≥ 15 cigarettes smoked per day

Dose	Duration
Pr Nicorette Invisipatch 25 mg/16 hours	First 8 weeks
Nicorette Invisipatch 15 mg/16 hours	Next 2 weeks
Nicorette Invisipatch 10 mg/16 hours	Last 2 weeks

Additional dosing information involving patch strengths of less than 25 mg (and therefore including possible use of NICORETTE gum) is provided below under the heading **Additional Dosing Schedules For the Patch Doses Lower than 25 mg**)

Missed Dose
If a dose is missed, the patch should be applied immediately and removed at bedtime. A new patch should be applied the next morning.

Administration of Patch
NICORETTE INVISIPATCH should be applied promptly upon its removal from the protective pouch to prevent loss of nicotine from the system. NICORETTE INVISIPATCH should be applied only once

a day to a non-hairy, clean, and dry skin site on the upper arm or the hip. A different site of application should be chosen each day. Each day a new NICORETTE INVISIPATCH system should be applied upon waking and removed at bedtime. It should not be worn for more than 16 hours/day.

Additional Dosing Schedules For the Patch Doses Lower than 25 mg:

For the convenience of the prescriber, dosing information involving the patch doses regulated by NHPD is provided below:

For those who smoke < 15 cigarettes per day:

- Use NICORETTE PATCH (nicotine transdermal system) in 15 / 10 / 5 mg strengths, available without a prescription.

Table 7: Recommended Dosage of NICORETTE® Patches for < 15 cigarettes per day	
Dose	**Duration**
NICORETTE® 15 mg/16 hours NICORETTE® 10 mg/16 hours NICORETTE® 5 mg/16 hours	First 6 weeks Next 2 weeks Last 2 weeks

Patch Treatment in combination with NICORETTE® 2 mg Gum

The NICORETTE patch system **(up to 15 mg ONLY)** can be used in combination with NICORETTE® 2 mg Gum if breakthrough cravings are experienced or there is difficulty in controlling cravings for cigarettes.

When used in combination with NICORETTE patch system and NICORETTE® 2 mg Gum should be taken as required, when cravings occur. It is recommended that a minimum of 5-6 pieces of gum are used daily. The maximum number of gums used in conjunction with the patch is 15 pieces per day.

Combination treatment should be used for 6 - 10 weeks, including a weaning period.

When NICORETTE patch system and 2 mg Gum are used in combination, weaning can be done by either (See Table 8):

1. Using the NICORETTE® INVISIPATCH 10 mg/16 hour for 2 weeks and then the NICORETTE® **Patch 5 mg/16 hour*** for 2 weeks while maintaining the number of pieces of 2 mg Gum that have been routinely used. Then when a patch is no longer used, the number of pieces of gum can be gradually reduced.
   OR
2. Stopping use of the NICORETTE® INVISPATCH 15 mg/16 hour and then gradually reducing the number of pieces of NICORETTE® 2 mg Gum that are being used.

Table 8: Recommended Dosage for Combination Treatment		
	Patch	**Gum**
Initial treatment period		
First 6 weeks	1 patch 15 mg/16 hours per day	*Ad libitum*

		Recommended 5 – 6 gums per day *Maximum 15 gums per* day
Weaning Period –Alternative 1		
Next 4 weeks	1 patch 10 mg/16 hours per day for 2 weeks Followed by 1 patch 5 mg/16 hours per day for 2 weeks*	*Ad libitum* Recommended 5 – 6 gums per day Maximum 15 gums per day
From then up to 6 months	Do not use the patch.	*Ad libitum* Recommended 5–6 gums per day Maximum 15 gums per day
Up to 12 months	Do not use the patch.	Gradually wean from gum use
Weaning Period - Alternative 2		
During the next 12 months	Do not use the patch.	Gradually wean from gum use

* NICORETTE Patch to be used for the 5 mg /16h patch, as there is not a 5 mg dose in the INVISPATCH system.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

There have been two reported cases of applying several nicotine patches simultaneously. Both people were attempting suicide and combined several nicotine patches, 21 mg, with other drugs. No serious effects resulted from either attempt.

Signs and symptoms of an overdose from NICORETTE INVISIPATCH (Nicotine Transdermal System) is expected to be the same as those of acute nicotine poisoning, including: pallor, cold sweat, nausea, salivation, vomiting, abdominal pain, diarrhea, headache, dizziness, disturbed hearing and vision, tremor, mental confusion and weakness. Prostration, hypotension, and respiratory failure may ensue with large overdoses. Lethal doses of nicotine produce convulsions quickly and death follows as a result of peripheral or central respiratory paralysis or, less frequently, cardiac failure. The acute, minimal, oral lethal dose of nicotine in non-tolerant human adults is believed to be 40 to 60 mg (<1 mg/kg). Much lower doses have been reported to be toxic in children.

Treatment: The NICORETTE INVISIPATCH system should be removed immediately if the patient shows signs of overdosage and the patient should seek immediate medical care by contacting a physician or local poison-control centre. The skin surface should be flushed with water and dried. **Soap must not be used since it may increase nicotine absorption.** Nicotine will continue to be delivered into the bloodstream for several hours after removal of the system because of a depot of nicotine in the skin.

Persons ingesting NICORETTE INVISIPATCH system should be referred to a health care facility for management. Due to the possibility of nicotine-induced seizures, activated charcoal should be administered. In unconscious patients with a secure airway, instill activated charcoal via a nasogastric tube. Repeated doses of activated charcoal should be administered as long as the system remains in the gastrointestinal tract since it will continue to release nicotine for many hours. A saline cathartic or sorbitol added to the first dose of activated charcoal may speed gastrointestinal passage of the system.

Other supportive measures include diazepam or barbiturates for seizures, atropine for excessive bronchial secretions or diarrhea, respiratory support for respiratory failure, and vigorous fluid support for hypotension and cardiovascular collapse.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

NICORETTE INVISIPATCH (Nicotine Transdermal System) are multilayered, laminated, flexible thin film patches containing nicotine as the active ingredient. NICORETTE INVISIPATCH has been specifically designed to provide a 16-hour rate-controlled delivery of nicotine following its application to intact skin. It is intended to be applied during the day and removed at night prior to sleeping, thus minimizing the potential for any sleep disturbances. NICORETTE INVISIPATCH provides nicotine without the other ingredients in tobacco smoke (e.g. tar, carbon monoxide, hydrogen cyanide) thereby attenuating abstinence symptoms associated with nicotine withdrawal during the cessation of smoking. NICORETTE INVISIPATCH increases the success rate of cessation in smokers who are motivated to quit.

Pharmacodynamics

Nicotine, the chief alkaloid in tobacco products, stereo-selectively binds to acetylcholine receptors at the autonomic ganglia, in the adrenal medulla, at neuromuscular junctions, and in the brain. Two types of central nervous system effects are believed to be responsible for nicotine's positively reinforcing properties. A stimulating effect, exerted mainly in the cortex via the locus ceruleus, produces increased alertness and cognitive performance. A "reward" effect via the "pleasure system" in the brain is exerted in the limbic system. At low doses the stimulant effects predominate while at high doses the reward effects predominate. Intermittent intravenous administration of nicotine activates neurohormonal pathways, releasing acetylcholine, norepinephrine, dopamine, serotonin, vasopressin, beta-endorphin, growth hormone and ACTH.

The cardiovascular effects of nicotine include peripheral vasoconstriction, tachycardia, and elevated blood pressure. Acute and chronic tolerance to nicotine develops from smoking tobacco or ingesting nicotine preparations. Acute tolerance (a reduction in response for a given dose) develops rapidly (less than one hour), but at distinct rates for different physiologic effects (skin temperature, heart rate, subjective effects). Withdrawal symptoms, such as cigarette craving, can be reduced in most individuals by plasma nicotine levels lower than those for smoking.

Withdrawal from nicotine in addicted individuals is characterized by craving, nervousness, restlessness, irritability, mood lability, anxiety, drowsiness, sleep disturbances, impaired concentration, increased appetite, minor somatic complaints (headache, myalgia, constipation, fatigue), and weight gain. Nicotine toxicity is dose-related and characterized by nausea, abdominal pain, vomiting, diarrhea, diaphoresis, flushing, dizziness, disturbed hearing and vision, confusion, weakness, palpitations, altered respiration, and hypotension.

Both smoking and nicotine can increase circulating cortisol and catecholamines, and tolerance does not develop to the catecholamine-releasing effects of nicotine.

Pharmacokinetics

The average amount of nicotine delivered to the patient from each NICORETTE INVISIPATCH system is approximately proportional to the surface area (69 μg/cm^2/hr). This results in systemic absorption of 10, 15 or 25 mg/day from the respective patch over a 16-hour period, as shown in Table 9.

Table 9: Systemic Absorption Of NICORETTE INVISIPATCH over 16 hours

Dose Absorbed (mg/16 hours)	System Surface Area (cm^2)	Total Nicotine Content (mg)	Approximate Cmax (ng/ml)
25	22.5	39.4	10
15	13.5	23.6	15
10	9.0	15.8	25

The dose of nicotine absorbed from the NICORETTE INVISIPATCH systems represents approximately 95% of the amount released in 16 hours. The remainder is lost via evaporation from the edge. About 40% of the total amount of nicotine remains in the patch 16 hours after application.

Following the first application of a NICORETTE system, plasma nicotine concentrations gradually increase to reach peak levels within 5-10 hours and then slowly declines until the system is removed, after which the terminal elimination half-life of nicotine is about 4 hours. The mean peak plasma of nicotine achieved with the 25 mg/day system is 24 – 25 ng/ml.

After repeated application of NICORETTE systems, plasma nicotine concentrations were not significantly higher than those after a single application, indicating no accumulation (see Table 10).

Table 10: Pharmacokinetics after repeated administration of Nicorette system: 15 mg/16 hour

Day (15 mg/16 hour System)	AUC (ng.h/mL)	AUC_{Inf} (ng.h/mL)	C_{MAX} (ng/mL)	t_g (h)	T_{MAX} (h)
1	12.2	13.0	13.0	3.7	8.0
6	12.2	12.9	14.2	3.4	6.0

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. Nicotine kinetics are similar following application of the patch on the arm and hip.

Combination Patch + Gum treatment

The plasma levels achieved when administering the maximum daily dosage of NICORETTE system (15 mg/16 hour) in combination with NICORETTE 2 mg Gum (24 pieces in 15 hours) were similar to those seen after administration of a maximum daily dose of NICORETTE 4 mg gum (19 pieces in 15 hours). The C_{trough} max value for the combination treatment (patch + 2 mg gum) was 39.4 ng/ml as compared to 38.1 ng/ml for the reference group (4 mg gum). Also, the maximum and minimum concentrations during the intense sampling time interval were similar for the combination treatment (38.3 and 35.4 ng/ml, respectively for Patch + Gum) and the reference treatment (40.0 and 33.4 ng/ml, respectively).

The total amount of nicotine released from the combined administration of maximum daily dosages of the patch (15mg/16 hour) and 2 mg gum (24 pieces in 15 hours) was somewhat lower than from the

administration of 19 NICORETTE® 4 mg gum over 15 hours (49.1 and 55.1 ng.ml respectively).

Absorption: Following removal of the NICORETTE system after 16 hours of wear, plasma nicotine concentrations decline in an apparently exponential fashion. The half-life after removal was about twice that observed after intravenous infusion, suggesting continued absorption from the skin depot. Patients had non-detectable nicotine concentrations within 10 to 12 hours after removing the system.

The average plasma nicotine level is about 20 to 36 ng/mL in moderate to heavy smokers. In comparison, the average plasma nicotine concentration in subjects delivered from NICORETTE® 15 mg/16 hour system is about 9 ng/mL. The average plasma nicotine concentration delivered from a single-dose of the Pr NICORETTE INVISIPATCH 25/mg/16 hour system is about 25 ng/mL.

Table 11: Steady state nicotine pharmacokinetic parameters for NICORETTE applied for 16 hours (N = 12)

	Mean ± SD (Range of Delivery Rate) (mg/day)		
	15*	**10**	**5**
C_{max} (ng/mL)	13.0 ± 3.1 (7.8 - 17.9)	6.9 ± 2.0 (4.8 - 10.0)	3.5 ± 0.7 (2.7 - 4.7)
C_{avg} 16 (ng/mL)	9.4 ± 2.4 (5.3 - 13.3)	4.9 ± 1.2 (3.0 - 6.8)	2.7 ± 0.5 (2.0 - 3.6)
C_{avg} 24 (ng/mL)	8.7 ± 2.1 (5.2 - 11.8)	4.8 ± 1.0 (3.3 - 6.3)	2.7 ± 0.4 (2.1 - 3.3)
C_{min} (ng/mL)	2.5 ± 0.8 (1.2 - 4.1)	1.4 ± 0.5 (0.5 - 2.4)	0.8 ± 0.3 (0.3 - 1.2)
T_{max} (hrs)	8 ± 3 (4 - 16)	9 ± 4 (6 - 16)	9 ± 4 (3 - 16)

C_{max}: maximum observed plasma concentration
C_{avg} 16: estimated average plasma concentration during the 0 to 16 hour period, calculated as AUC (0-16)/16
C_{avg} 24: average plasma concentration calculated over 24 hrs
C_{min} : minimum observed plasma concentration
T_{max}: time of maximum plasma concentration
* Data for 15 mg system are derived from a different study than the 5 and 10 mg systems.

There are no differences in nicotine kinetics between men and women using NICORETTE systems. Linear regression of both AUC and C_{max} versus total body weight shows the expected inverse relationship. Men and women having low body weight are expected to have higher A_{UC} and C_{max} values.

Distribution: The volume of distribution following i.v. administration of nicotine is approximately 2 to 3 L/kg and the half-life ranges from 1 to 2 hours. Plasma protein binding of nicotine is <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.

Metabolism: The major elimination organ is the liver, and average plasma clearance is about 1.2 L/min; the kidney and lung also metabolize nicotine. There is no significant skin metabolism of nicotine. More than 20 metabolites of nicotine have been identified, all of which are believed to be less active than the parent compound. 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.

Excretion: The primary urinary metabolites are cotinine (15% of the dose) and trans-3-hydroxycotinine (45% of the dose). Usually about 10% of nicotine is excreted unchanged in the urine. As much as 30% may be excreted unchanged in the urine with high urine flow rates and acidification below pH 5.

Special Populations and Conditions

Pediatrics: NICORETTE® INVISPATCH is contraindicated in persons under 18 years of age.

Geriatrics: The initial dose in elderly patients may have to be adjusted because concomitant diseases may increase risk.

Gender: There are no differences in nicotine kinetics between men and women using NICORETTE systems. Linear regression of both AUC and Cmax versus total body weight shows the expected inverse relationship. Men and women having low body weight are expected to have higher AUC and Cmax.

STORAGE AND STABILITY

Do not store above 25°C. Protect from light.

Once removed from the protective pouch, NICORETTE® INVISPATCH (Nicotine Transdermal System) should be applied promptly since nicotine is volatile and the system may lose strength.

SPECIAL HANDLING INSTRUCTIONS

Once removed from the protective pouch, NICORETTE INVISIPATCH (Nicotine Transdermal System) should be applied promptly since nicotine is volatile and the system may lose strength.

The amounts of nicotine that are tolerated by adult smokers can cause severe poisoning and even prove fatal if the NICORETTE INVISIPATCH systems are applied or ingested by children or pets. Used NICORETTE INVISIPATCH systems contain approximately 40% of their initial nicotine content. Therefore, patients should be cautioned to keep both the used and unused NICORETTE INVISIPATCH systems out of the reach of children and pets.

NICORETTE INVISIPATCH systems can be a dermal irritant and can cause contact sensitization. Care should be taken to avoid unnecessary contact with active systems. If you do handle active systems, wash with water alone since soap may increase nicotine absorption. Do not touch your eyes.

Disposal of used patches

When the used system is removed from the skin, it should be folded over and placed in its pouch. The used system should be disposed of immediately in such a way as to prevent its access by children or pets (see **Part III CONSUMER INFORMATION** for further directions on handling and disposal).

DOSAGE FORM, COMPOSITION AND PACKAGING

NICORETTE INVISPATCH is available in three strengths/sizes. The average amount of nicotine delivered to the patient from each NICORETTE INVISIPATCH system is approximately proportional to the surface area of each system and results in systemic absorption of 10 mg (9 cm2), 15 mg (13.5 cm2) and 25 mg (22.5 cm2), respectively, from each of the patches over a 16 hour period as shown in Table 12. Each patch contains nicotine at a concentration of 1.75 mg/cm2. Other ingredients are polyester (non woven), polybutene and polyisobutylene.

A single patch comes in a foil pouch. NICORETTE INVISPATCH systems are labeled with the average amount of nicotine delivered by the patch over 16 hours and are available in packages of 7 and 14 patches.

Table 12: Composition and availability of NICORETTE INVISIPATCH systems			
Strength	**Dose Delivered (mg/16 hours)**	**System Surface Area (cm^2)**	**Total Nicotine Content (mg)**
25	25	22.5	39.37
15	15	13.5	23.62
10	10	9.0	15.75

NICORETTE INVISIPATCH is composed of four different layers, as can be seen in Figure 1. (not drawn to scale).

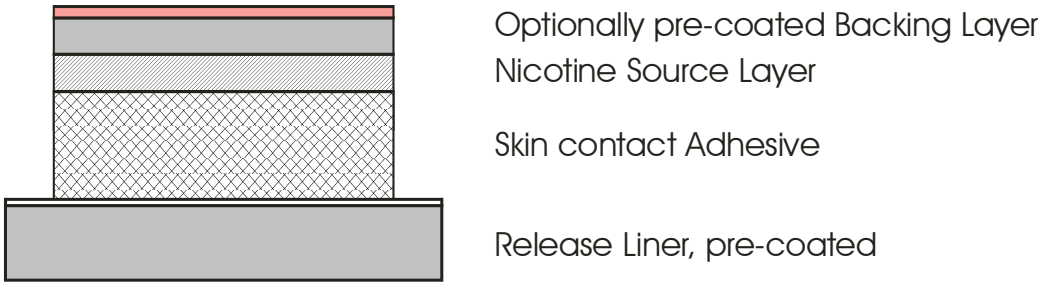


Figure 1: Schematic cross section of NICORETTE INVISIPATCH

The backing layer protects the system from the environment and gives structural support and consists essentially of polyethylene terephthalate, a rigid and diffusion-resistant polymer. The nicotine source layer consists initially of nicotine, basic butylated methacrylate copolymer and medium-chain triglycerides. The acrylic adhesive contains Durotak 387-2051, a pressure-sensitive adhesive, as the principle ingredient. The release liner, again consisting of polyethylene terephthalate, is removed prior to use.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

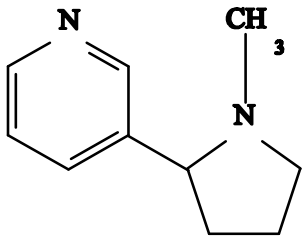
Proper name: nicotine

Chemical name:

***S*-3-(1-methyl-2-pyrrolidinyl) pyridine**
1-methyl-2-(3-pyridyl) pyrrolidine
ß-pyridyl-∝-N-methylpyrrolidine

Molecular formula and molecular mass: $C_{10}H_{14}N_2$ 162.23

Structural formula:



Physicochemical properties: Nicotine is a clear, colorless to pale yellow oily liquid with an unpleasant pungent odor; it is volatile, hygroscopic, and turns brown on exposure to air or light. Nicotine is miscible with water below 60°C; very soluble in alcohol, chloroform, ether, petroleum ether, kerosene and oils. The pK_a is 3.04 and 7.84 (at 15°C) and the pH is 10.2 (0.05 M solution) while the Octanol-water partition coefficient is 15:1 at pH 7. The boiling point is 247ºC (at 745 mm Hg) with partial decomposition at 123-125ºC (at 17 mm Hg).

CLINICAL TRIALS

Clinical Trial in Support of the 25 mg Patch
The efficacy and safety of the 25 mg patch was assessed in a double-blind placebo-controlled study, undertaken in 36 centers across Europe in conjunction with the European Respiratory Society, and known as the Collaborative European Antismoking Evaluation (CEASE) study. A total of 3575 smokers were randomized; inclusion criteria included smoking at least 15 cigarettes per day (cpd). The mean baseline cpd for the total study population was 27 ±10.

The primary efficacy variable (ie "success in quitting smoking") was biochemically-verified, self-reported continuous abstinence from Week 2 of treatment initiation to Week 52 (ie seven visits). Biochemical verification was defined as less than 10 ppm exhaled carbon monoxide in expired air. Smokers were randomized into 5 arms: shorter duration full-dose treatment (8 weeks) for each of 15

and 25 mg patch; longer duration full-dose treatment (22 weeks) for each of the two patch doses; and placebo. For all treatment arms, there was an additional four week tapering period at the end of the designated treatment duration. Intent-to-treat population was used, and all subjects with missing data, for whatever reason, were defined as treatment failures. Subjects did not have to remain on treatment for the specified duration in order to be eligible as "abstinent from smoking", provided they remained in the study.

Results:

Quit Rates, Week 52, all arms:

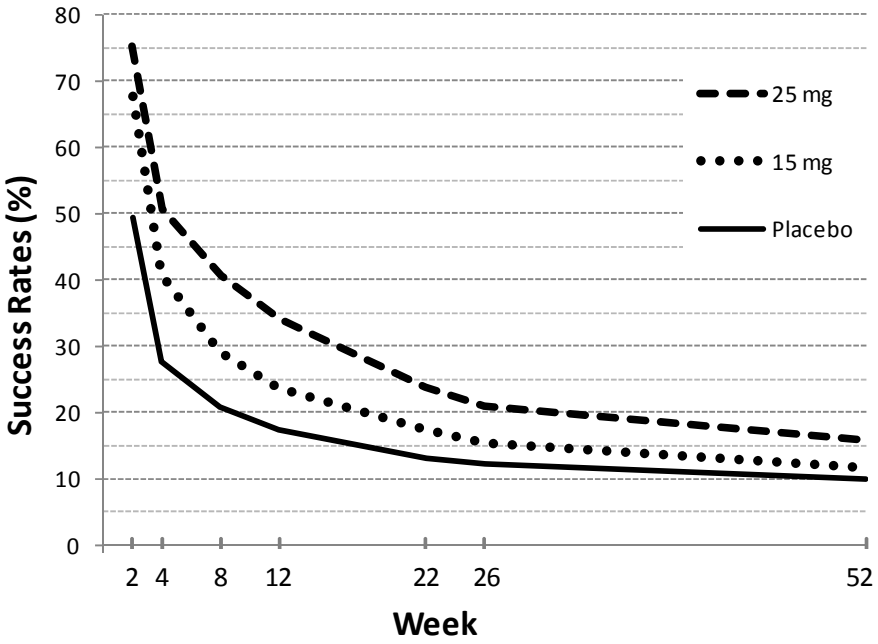
25 mg/ 8 weeks	**15 mg 8 weeks**	**25 mg/ 22 weeks**	**15 mg 22 weeks**	**Placebo**
15.9% (114 /715)	11.7% (84 /716)	15.4% (110 /715)	13.7% (98 /715)	9.9% (71 /715)

-The quit rate for the 25 mg patch/8 weeks is statistically higher than that for the 15 mg patch/8 weeks (15.9% vs 11.7% respectively, p = 0.0210)

-There is no evidence of benefit from longer use of the patch for either dose, based on Week 52 data.

The quit rate curve for all visits up to Week 52 is presented below, for the following three arms: 25 mg/8 weeks; 15 mg/8 weeks; placebo.

Figure 2. Quit Rates, Week 2 through 52, for CEASE trial



Quit rates at selected time points, including all follow-up visits, are presented below in Table 13

Table 13: Quit rates for 25 mg vs. 15 mg (8 weeks treatment) vs. Placebo						
Treatment Group	**Number of Patients**	**Quit Rates (%)** Time point in Study				
		4 Weeks	**6 Months**	**1 Year**	**18 Months**	**24 Months**
[PR]NICORETTE 25 mg, 8 weeks	(n=715)	50.6	21.0	15.9	13.3	11.2
NICORETTE 15 mg, 8 weeks	(n=716)	40.9	15.5	11.9	10.2	8.7
Placebo	(n=715)	27.6	12.0	9.8	8.4	7.1

Pivotal Comparative Bioavailability Study

A randomized, two-period, two-way crossover comparative bioavailability study was performed on 30 male and female subjects smoking a minimum of 15 cigarettes per day for at least one year. Subjects were not permitted to smoke during the conduct of the study. The rate and extent of absorption of nicotine was measured and compared following a single 16-hour patch application of NICORETTE® (10 +15 mg/16 hours) and [Pr]NICORETTE® Invisipatch™ (25 mg/16 hours). The results from measured data are summarized below.

Table 14 **Nicotine** **(25 mg/16 hr)** **Geometric Mean[#]** **Arithmetic Mean (CV %)**				
Parameter	**[Pr]NICORETTE INVISIPATCH [*]**	**NICORETTE [†]**	**Ratio of Geometric Means[#]**	**90% Confidence Interval**
AUC_{0-16} (h*ng/mL)	241.0 249.4 (25)	240.4 246.4 (26)	100	92-109
AUC_T (h*ng/mL)	302.6 311.8 (23)	315.2 322 (23)	96	89-103
AUC_I (h*ng/mL)	306.4 315.8 (23)	320.8 327.8 (23)	96	89-103
C_{max} (units)	23.6 24.3 (23)	21.5 21.9 (17)	109	101-118
T_{max} [§] (h)	8.8 (25)	8.6 (28)		
$T_{½}$ [§] (h)	2.8 (19)	3.0 (20)		

[*] [Pr]NICORETTE® Invisipatch™ (1x25 mg/16 hours)
[†] NICORETTE® (10 +15 mg/16 hours)
[§] Expressed as the arithmetic mean (CV%) only
[#] Based on the least-square means estimate

DETAILED PHARMACOLOGY

Nicotine was first isolated from tobacco in the early 1900s and its actions are now well established. The drug acts directly on sympathetic and parasympathetic ganglia, producing initial stimulation, followed by depression, due to blockade of transmission. It has a wide variety of stimulant and depressant properties, including central stimulating effects (EEG activation, behavioral wake up, tremor and convulsions, vomiting, effects on learning, temperature reduction), cardiovascular actions (increased heart rate and blood pressure), respiratory stimulation, stimulation, followed by depression of GI motility and increased release of adrenaline, insulin, ACTH and cortisol. Tachyphylaxis develops quickly to the actions of nicotine and tolerance on chronic treatment has been shown to occur for many, but not all, effects.

TOXICOLOGY

Only dermal irritation studies were performed with NICORETTE® since the toxic effects of nicotine in animals have been well-documented in the literature.

Acute Toxicity:

The acute toxicity of nicotine reported in the literature is summarized in the Table 15

Table 15: Acute Toxicity

Species	Route	Dose (mg/kg)	Response
Mouse	Oral	24	LD_{50}
	s.c.	16	LD_{50}
	i.v.	7.1	LD_{50}
	i.p.	63.5	LD_{50}
Rat	oral	50-60	Approx. LD_{50}, convulsions, paralysis
Rabbit	i.v.	9.4	LD_{50}
	dermal	50	Estimated LD_{50}
Dog	i.v.	5	LD_{50}
Cat	i.v.	2	LD_{50}

The oral LD_{50} for nicotine in rodents varies with species, but is in excess of 24 mg/kg. Death is due to respiratory paralysis.

Carcinogenicity and Mutagenicity Studies

Nicotine itself does not appear to be a carcinogen in laboratory animals. However, nicotine and its metabolites increased the incidences of tumors in the cheek pouches of hamsters and fore-stomach of F344 rats, respectively, when given in combination with tumor initiators. One study, which could not be replicated, suggested that cotinine, the primary metabolite of nicotine, may cause lymphoreticular sarcoma in the large intestine of rats.

Nicotine and cotinine were not mutagenic in the Ames Salmonella test. Nicotine induced repairable DNA damage in an E.coli test system. Nicotine was shown to be genotoxic in a test system using Chinese hamster ovary cells.

Reproduction and Teratogenicity Studies

In rats and rabbits, implantation can be delayed or inhibited by a reduction in DNA synthesis that appears to be caused by nicotine. Studies have shown a decrease in litter size in rats treated with nicotine during gestation.

Nicotine has been shown to produce skeletal abnormalities in the offspring of mice when given doses toxic to the dams (25 mg/kg subcutaneously or intraperitoneally). This is approximately 100 times the daily human dose of NICORETTE® 15 mg/day. Studies in rats and monkeys have not demonstrated a teratogenic effect of nicotine at doses which occur during cigarette smoking.

Nicotine teratogenicity has not been studied in humans except as a component of cigarette smoke (each cigarette smoked delivers about 1 mg of nicotine). It has not been possible to conclude whether cigarette smoking is teratogenic to humans.

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PART III: CONSUMER INFORMATION

[Pr] NICORETTE INVISIPATCH Nicotine Transdermal System
25 mg/ 16 hr

This leaflet is part III of a three-part "Product Monograph" published when the NICORETTE INVISIPATCH system was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about NICORETTE INVISIPATCH. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
[PR]NICORETTE INVISIPATCH 25 mg/16 h is a prescription strength skin patch containing nicotine which can help motivated adults stop smoking when used as part of a comprehensive stop-smoking program. Although it may be an effective aid, it is only one part of your stop smoking program.

The entire process is a stepwise 12 week program to decrease the amount of nicotine you got from smoking, specifically:

- Step 1: 25mg/16hr
- Step 2: 15mg/16 hours
- Step 3: 10mg/16hours.

See the **Proper Use of this Medication** section for more information on how and when to apply the patch.

The 15 and 10mg strength are available without a prescription as natural health products.

The 25 mg patch is for people who smoke **at least** 15 cigarettes per day.

What it does:
When you put NICORETTE INVISIPATCH on your skin, nicotine passes from the patch through the skin and then into your blood. This replaces some of the nicotine you crave from cigarettes and therefore can help to relieve withdrawal symptoms associated with quitting smoking

When it should not be used:
Do not use NICORETTE INVISIPATCH if you:

- are hypersensitive or allergic to nicotine or any ingredient in the patch (see list below)
- are using CHAMPIX (varenicline), a prescription medication for quitting smoking. The combination of CHAMPIX and NICORETTE INVISIPATCH is not expected to improve your chances of quitting, and may result in more side effects than with nicotine replacement systems alone.
- have heart problems, including heart attack (myocardial infarction) or stroke, irregular heart beat (arrhythmia), severe or worsening heart pain (angina), or heart disease.
- are under 18 years old
- have generalized skin disorders
- are pregnant or nursing
- are an occasional or non-smoker

Pregnant and Nursing women
Nicotine in any form may cause harm to your unborn baby if you use nicotine while you are pregnant. Do not use NICORETTE INVISIPATCH if you are pregnant or nursing. Be careful not to become pregnant while using NICORETTE INVISIPATCH. If you think you might be pregnant, do not use NICORETTE INVISIPATCH until you have talked to your doctor.

What the medicinal ingredient is:
Nicotine

What the nonmedicinal ingredients are:

- acrylic adhesive containing Durotak 387-2051,
- Butylated methacrylate copolymer and medium-chain triglycerides,
- polyethylene terephthalate
- croscarmellose sodium
- aluminum acetylacetonate

What dosage forms it comes in:
Transdermal system (patch applied to the skin)

The 25 mg/16 hr [Pr] NICORETTE INVISIPATCH is available by prescription only.

WARNINGS AND PRECAUTIONS

NICORETTE INVISIPATCH should **be kept out of the reach of children and pets, as there is enough nicotine to cause severe poisoning and even death.**

BEFORE you use NICORETTE INVISIPATCH **talk to your doctor or pharmacist if** you have:

- allergy to any type of glue or bandage
- an ulcer
- atopic or eczematous dermatitis
- high blood pressure
- history of any kind of heart or circulation problem
- hyperthyroidism
- insulin-dependent diabetes
- kidney disease

- liver disease
- pheochromocytoma(a type of tumor)
- or are over 60 years old

The NICORETTE INVISIPATCH should be removed 2 hours before engaging in prolonged strenuous exercise. This is because the increase in skin temperature and blood flow with prolonged sustained exercise may cause your body to absorb more nicotine than usual.

You should not wear the NICORETTE INVISPATCH into the hotub, sauna, hot whirlpool spa bath; if you are sunbathing; or if you are using heating pads, electric blankets, heated water beds, heat lamps or hot water bottles**.** High temperatures may cause your body to absorb more nicotine than usual. For the same reason, you should also be cautious and watch for any unusual side effects if you develop a fever.

Remove the NICORETTE INVISIPATCH prior to undergoing any Magnetic Resonance Imaging (MRI) procedures to prevent the risk of burns.

INTERACTIONS WITH THIS MEDICATION

DO NOT smoke, chew tobacco, use snuff or any other form of nicotine while using the NICORETTE INVISIPATCH because you may absorb more nicotine than your body is used to, and this excess could cause harm.

Unlike other strengths, the prescription strength [PR] NICORETTE INVISIPATCH 25 mg/16 hrs should NOT be used in combination with NICORETTE 2 mg gum as this may result in overdose of nicotine.

Symptoms of nicotine overdose include: nausea, abdominal pain, vomiting, diarrhea, cold sweat, dizziness, disturbed hearing and vision, mental confusion, marked weakness, rapid heartbeat or difficulty breathing (see also the OVERDOSE section)

Drugs that may interact with NICORETTE INVISIPATCH include:

- acetaminophen
- caffeine
- Champix (smoking cessation aid)
- imipramine (eg anti-depressant)
- insulin
- isoproterenol (for treating heart block or asthma)
- labetolol (for high blood pressure)
- oxazepam (sedative)
- pentazocine (pain medication)
- phenylephrine (decongestant)
- prazosin (for high blood pressure)
- propanolol (for high blood pressure)
- theophylline (eg for asthma)

Smoking may alter the effects of some medicines. Once you have quit smoking, it may be necessary for your doctor to adjust the doses of medicines you may be using. Therefore, it is important to tell your doctor or pharmacist about ALL medicines you are taking and consult them before you use NICORETTE INVISIPATCH. (See also the WARNINGS AND PRECAUTIONS section above)

PROPER USE OF THIS MEDICATION

Do not use NICORETTE INVISIPATCH if the **pouch is damaged or opened.**

General Considerations:

NICORETTE INVISIPATCH is applied when you wake up each day and worn during your waking hours for 16 hours. The patch is removed at bedtime or 16 hours after you applied it, in order to allow a patch-free period while you sleep.

- Stop smoking completely before you start using NICORETTE INVISIPATCH.
- Do not smoke even when you are not wearing the patch, as the nicotine in your skin will still be entering your bloodstream for several hours after you take the patch off.
- Do not use more than one patch at a time, as this may cause nicotine overdose
- The 25 mg [Pr]NICORETTE INVISIPATCH is not to be used in combination with NICORETTE Gum
- Do not use the 25 mg [Pr]NICORETTE INVISIPATCH for more than 8 consecutive weeks or the complete NICORETTE stepwise smoking cessation system for more than 12 consecutive weeks without consulting a doctor (see Usual Dose below).
- Stop using NICORETTE INVISIPATCH and consult your doctor if you think you are pregnant when on the smoking cessation program.
- Exercising strenuously or exposure to extreme heart (e.g. saunas, hot tubs) can cause an increase in nicotine absorption into your blood. Remove the patch before any of these activities.
- Not all adhesive products stick to all people. If the patch does not stick well or loosens after applications, tape only the edges down with first aid tape.

Usual Dose:

For those who smoke at least 15 cigarettes per day:

Step 1: Establish your quit date and do not smoke before you put your first patch on. You will begin treatment with the 25 mg [Pr] NICORETTE INVISIPATCH. Use 1 patch

daily for 8 weeks.

Step 2: Begin your weaning phase by using the 15 mg NICORETTE product for 2 weeks.

Step 3: Complete your weaning phase by using the 10 mg NICORETTE product for 2 weeks.

Recommended Dosage for at least 15 cigarettes smoked per day	
Dose	**Duration**
Pr NICORETTE INVISIPATCH 25 mg/16 hours	First 8 weeks
NICORETTE 15 mg/16 hours	Next 2 weeks
NICORETTE 10 mg/16 hours	Last 2 weeks

Nicorette Gum (2 mg) can be used in combination with the two lower doses of patches (10 and 15 mg) to help deal with cravings; see the leaflets for those products for more information.

For those who smoke less than 15 cigarettes per day:
The 25 mg Pr NICORETTE INVISPATCH is not for you. Instead, start with 15 mg dose (see the leaflet instructions for that dose).

Where to apply NICORETTE INVISPATCH
Select a location for application of NICORETTE INVISIPATCH, on a healthy non-hairy, clean, dry area of the upper part of your arm, or your back, shoulder or hip. Do not shave the area, as this may be irritating to the skin, when the patch is applied. Do not put the NICORETTE INVISIPATCH, on skin that is very oily, inflamed, swollen, red, burned, broken out, cut, or irritated in any way, since these conditions may alter the amount of drug absorbed.

How to apply NICORETTE INVISPATCH
You should put on a new NICORETTE INVISIPATCH each day at about the same time after you wake up so that you don't forget. The patch should be removed at bedtime to provide a patch-free (nicotine-free) period. Do not wear it for more than 16 hours each day.

1. Each patch is sealed in its own protective pouch. Do not remove the NICORETTE INVISIPATCH, from the pouch until you are ready to use it because it will lose strength if stored out of the pouch. Using scissors, cut along the dotted line to open the pouch. Save the pouch, because you will use it when throwing away the NICORETTE INVISIPATCH, at bedtime (see 6).

2. A clear protective release liner covers the sticky side of the NICORETTE INVISIPATCH - the side that will be put on your skin. The liner has a partial cut in it to help you remove it from the patch. With the sticky side facing you, pull the liner away from the NICORETTE INVISIPATCH. Try not to touch the adhesive surface with your hands.

3. Immediately apply the sticky side of the NICORETTE INVISIPATCH, to your skin on a clean, dry, non-hairy portion of your upper arm, shoulder, back or hip. Firmly press down on the patch and rub it with your palm for 10-20 seconds to ensure that the patch sticks well especially around the edges.

If the NICORETTE INVISPATCH falls off, put a new one on a different skin area that is clean and dry. Remove the new patch, as usual, at bedtime.

4. Rinse your hands with water (DO NOT USE SOAP, soap increases the absorption of nicotine) when you have finished applying the NICORETTE INVISIPATCH, Nicotine on your hands could get into your eyes and nose and could cause stinging, redness, or more serious problems.

5. After wearing the patch, remove it before you go to bed or no longer than 16 hours from when you first applied it, thus allowing for a patch-free period during sleep. Fold the used patch in half with the sticky side together. Place it in its pouch (kept from the morning application) or place it in a piece of aluminum foil. Dispose of the used patch out of the reach of children and pets.

6. The next day, choose a different place on your skin to apply a new NICORETTE INVISIPATCH, and repeat 1-6 above. The same area should not be used again for at least one week.

7. Not all adhesive products stick to all people. If the patch does not stick well, or loosens after application, tape only the edges down with first aid tape.

Water and NICORETTE PATCH
The NICORETTE INVISIPATCH generally adheres firmly to the skin, so you may keep it on while bathing, swimming or showering.

Overdose:
Remove the nicotine patch and consult your doctor if you experience symptoms of overdose, including severe headaches, dizziness, severe stomach upset (indigestion, heartburn), cold sweats, blurred vision, weakness, fainting, mental confusion, irregular heart beat, chest pain, palpitations

In case of drug overdose, contact your regional poison control centre immediately even if there are no symptoms.

Missed Dose:
If you forget to put your patch on in the morning, put it on as soon as you remember. Remove it at bedtime. Put on a

new patch the next morning.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medications, NICORETTE INVISIPATCH, can cause some side effects. For most patients these side effects are likely to be minor and temporary. However, some may be serious.

The most common side effects experienced with NICORETTE INVISIPATCH are:

- constipation
- dry mouth
- feeling nervous
- headache
- indigestion
- mild redness, itchiness, burning at the application site
- sleeping problems

When you first put on NICORETTE INVISIPATCH, mild itching, burning or tingling is normal and should go away within an hour.

After you remove NICORETTE INVISIPATCH, the skin under the patch might be somewhat red. Your skin should not stay red for more than one day.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Seek immediate emergency medical assistance
		Only if severe	In all cases	
Uncommon	Symptoms of nicotine overdose, including: cold sweat, dizziness, disturbed hearing and vision, mental confusion, marked weakness, abdominal pain/nausea/vomiting, rapid heartbeat or difficulty breathing			✓
	Symptoms of allergic reaction, including: rash, severe itching/ redness, swelling, or trouble breathing			✓
	Heart palpitations (fast or unusual heart beat)			✓
	Unusual leg pain			✓

Stop using NICORETTE INVISIPATCH and contact your doctor immediately if you have an allergic reaction (including skin rash, hives, swelling, very red skin, trouble breathing) or any severe or unusual side effects. Remove the patch and, wash the area with water (do not use soap) . Do not put on a new patch. You may be allergic to one of the components of the NICORETTE INVISIPATCH. If you do become allergic to the NICORETTE INVISIPATCH you could get sick from using cigarettes or other nicotine-containing products.

This is not a complete list of side effects. For any unexpected effects while using NICORETTE

INVISIPATCH, ***contact your doctor or pharmacist.***

HOW TO STORE IT

NICORETTE INVISIPATCH can be poisonous and extremely dangerous to children or pets if applied to the skin or swallowed. Keep used and new NICORETTE INVISIPATCH systems out of the reach of children and pets.

Keep each NICORETTE INVISPATCH in its protective pouch until you are ready to use it because the patch will lose nicotine into the air if it is stored outside the pouch.

Do not store above 25°C. Protect from light.

Remember, the inside of your car can reach temperatures much higher than this in the summer.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701D
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, McNeil Consumer Healthcare, division of Johnson & Johnson Inc. at 1-800-611-5889.

Questions about NICORETTE INVISIPATCH 1-866-311-5655

Product Monograph available to doctors and pharmacists upon request.

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