drug information perspectives

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Contents

NICOTINE

TRADE NAME(S): Habitrol, Nicoderm, Nicorette Gum, Nicorette Inhaler, Nicorette Lozenge, Thrive

CLASSIFICATION: Nicotinic acetylcholine receptor agonist; smoking cessation aid

ACTION

Agonist at nicotinic acetylcholine receptors in the autonomic ganglia, neuromuscular junction, adrenal medulla and brain. Reduces the withdrawal symptoms during smoking cessation by partially substituting for the nicotine in tobacco products. Nicotine activates the nucleus accumbens reward system by increasing dopamine release. May also provide, in a less toxic manner, the same benefits as tobacco on alertness, mood and coping.

Produces transient stimulation and then blockade of transmission at autonomic ganglia and the neuromuscular junction. Small doses stimulate autonomic ganglia, and produce release of catecholamines from the adrenal medulla, while larger doses block autonomic transmission and catecholamine release from the adrenal medulla.

In the brain, low doses of nicotine stimulate the cerebral cortex and higher doses stimulate the reward system; toxic doses lead to tremors and seizures.

Directly stimulates the chemoreceptor trigger zone to produce emesis.

Increases blood pressure, heart rate and cardiac work by stimulation of sympathetic ganglia, catecholamine release from the adrenal medulla, and other mechanisms. Increases the release of acetylcholine, noradrenaline, serotonin, dopamine, beta-endorphin, vasopressin, growth hormone and ACTH.

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PHARMACOKINETICS

	Cmax (ng/mL) (1 dose)	Tmax (min)	Bioavailability %	Cmax (ng/mL) (steady-state)
Cigarette	15-30	3-5	80-90	44*
Gum 2mg	6-9	30	78	25**
Gum 4mg	10-17	30	55	50**
Inhaler 4mg	8	30	55	20-25***
Lozenge 2mg	4	60	50	13****
Lozenge 4mg	11	60	79	26****
Patch 14-21mg	11-23	3-12hours	75-100	8-23

* 1 cigarette every 30 minutes
** 1 piece chewed every 30 minutes
*** 20 minute inhalation every hour for 12 hours
**** one lozenge every 1.5 hours

Half-life: 2 hours (from cigarettes, gum, inhaler, lozenge); 3-4 hours (after removal of transdermal patch)
Absorption: Nicotine is a weak base and its absorption depends on pH; replacement products are buffered to an alkaline pH to increase absorption. Well absorbed from skin, lungs and buccal mucosa; absorption from lungs and buccal mucosa avoids first-pass liver metabolism. Poorly absorbed from the GI tract. ***Gum***: Absorbed mainly by buccal mucosa; small amount in GI tract. Degree of absorption depends on how vigorously and how long it is chewed. Unchewed, swallowed gum has only 15% absorption due to poor GI absorption and first-pass liver metabolism. Food, liquids and especially acidic drinks decrease absorption. ***Inhaler***: Mainly absorbed through buccal mucosa; 20% swallowed; 13% trachea/esophagus/bronchi; 5% reaches the lungs. Increased absorption with higher temperatures. ***Lozenge***: Mainly buccal absorption with some oral ingestion. Completely dissolves in 20-30 minutes. ***Patch***: Lag-time of 1 hour before nicotine appears in blood and absorption continues after removal because of depot in skin. Lower AUC in obese patients. Heat increases absorption.
Distribution: Plasma protein binding less than 5%. Widely distributed Vd 2-3 L/kg.
Metabolism: 80-90% metabolized in the liver, and also in lungs and kidney, to cotinine (major metabolite) and many other less active metabolites. Main enzyme is CYP2A6; possible minor involvement by CYP2B6, 2E1, 2D6, 2A13.
Elimination: As parent drug (10-20%) and metabolites in urine; increased elimination as parent drug in acidic urine. Clearance is proportional to hepatic blood flow; increased clearance after a meal, decreased clearance while sleeping, higher clearance in pregnancy.
Special populations:
Elderly: Decreased clearance, decreased renal clearance, increased AUC.
Renal impairment: Moderate impairment: Decreased clearance and non-renal clearance, increased AUC. Severe impairment: Decreased clearance, increased half-life, increased AUC, decreased renal and non-renal clearance.
Sex difference: None detected.
Pharmacogenetics: Polymorphisms in CYP2A6 and the other involved enzymes may reduce metabolism.

USES AND EFFICACY
Uses: A temporary aid in smoking cessation, with or without behavioural therapy. Reduces the symptoms of nicotine withdrawal by partially substituting for the nicotine in cigarettes. Increases the odds of quitting 1.5- to 2-fold. Abstinence rates after one year are approximately 17% with nicotine replacement versus 10% in the control group.

May be used as a temporary substitute for smoking; for example, in airplanes or other areas where smoking is not allowed.

Major clinical trials
Transdermal patch safety in patients with acute coronary syndromes: A cohort study was conducted in smokers who had been admitted with an acute coronary syndrome. Patients who received transdermal nicotine replacement starting in hospital were matched to those who did not (n=187 in each group). The study had 80% power to detect a 2% increase in mortality at 7 days and a 4% increase in mortality at 1 year. There was no difference in mortality at 7

days, 30 days or 1 year.[Am J Cardiol 2005; 95(8):976-978.] Study limitations: Small study size; the analysis is based on a very small number of deaths, 9-10 in each group at one year.

Reduce-to-Quit Gradual Reduction: A randomized, placebo-controlled double-blind study in 3297 mild-severe smokers used a 2-phase method of smoking cessation with nicotine gum. In the first 8-week phase, smokers gradually reduced smoking while increasing gum use: on the first day, they substituted one piece of gum for their first cigarette, and each subsequent day they tried to substitute one more piece of gum for smoking. Heavier smokers used the 4mg dosage form. Once they had achieved 24-hour smoking abstinence, smokers entered the second phase using established smoking cessation guidelines for nicotine gum. Abstinence for 24-hours was achieved after a median of 29 days. Both 28-day continuous abstinence rates and 6-month abstinence rates were higher in the active treatment group (10.3% versus 3.9% with placebo for 28-days; 5.9% versus 2.1% for 6-months). Cardiovascular adverse events had a similar incidence in active and control groups (0.4%). [American Journal of Preventive Medicine 2009;36(2):96-104.]

Clinical course: Nicotine absorbed from cigarettes reaches the brain in 10-20 seconds. All nicotine replacement products lack this rapid onset of effect (see PHARMACOKINETICS) and therefore do not eliminate all symptoms of withdrawal. However, craving for cigarettes is reduced from the first day of therapy.

Place in therapy
Of marginal benefit for smoking cessation. Unfortunately, 80% of patients are still smoking one year after their "quit date". Success does not depend on dosage form, setting, duration of therapy or type of support. Women may have lower cessation rates than men.

Advantages:
- Available without a prescription
- Usually well-tolerated
- Different dosage forms available

Disadvantages:
- Patient may become dependent

Comparisons:
The gum, inhaler, lozenge and patch are equally effective for achieving smoking abstinence. Choice of product should be individualized. The patches have the highest compliance rate (82%), are easiest to use, can be used without regard to drinking and eating, are discrete, lack local oral irritant effects and do not reinforce the behavioural action of smoking, but can still cause systemic toxicity, and may irritate the skin. As well, patients cannot titrate the amount and timing of each dose. The gum is discrete to use and timing can be controlled, but it may cause oral irritation, is initially unpleasant and hard to chew, cannot be taken with coffee and other drinks, and theoretically it may be easier for patients to become dependent on it. Lozenges are similar but more discrete and not a problem to chew. The inhaler most closely mimics the act of smoking, is not discrete to use, and can irritate the mouth and throat. Combining products, e.g. patch plus ad lib gum, is considered more effective than one product alone.

Versus bupropion:
Bupropion is equally or more effective than nicotine replacement. In a randomized, placebo controlled study, one-year abstinence rates were 15.6% with placebo, 16.4% with nicotine patches, 30.3% with bupropion, and 35.5% with the two combined (not significantly different from bupropion alone). The incidence of weight gain is the same. The combination of bupropion and nicotine replacement is under investigation; generally it has not been found to be more effective than bupropion alone but may be useful in some patients.

Versus varenicline:
Varenicline may be equally or more effective than nicotine replacement, based on indirect comparisons. In a randomized open trial, one-year abstinence rates were not significantly different, 26.1% with varenicline and 20.3% with nicotine patches. Varenicline caused more nausea, headache, abnormal dreams, constipation, dizziness, and disturbed attention. There was no difference in weight gain.

Investigational/Unapproved uses
Agitation in patients with dementia: Case reports suggest reduced agitation and inappropriate behaviour.
Akathisia due to antipsychotic drugs: Patches reduced akathisia in one study.
Mental illness/substance abuse: Patients with mental illness or additional substance abuse disorders may have high levels of nicotine dependence and may require high or prolonged doses.
Tourette`s syndrome: The addition of nicotine patches to haloperidol therapy may reduce behavioural symptoms including tic severity; mixed results.
Ulcerative colitis: In a randomized, placebo-controlled trial in mild-moderate ulcerative colitis, clinical improvement was seen in 39% of patients treated with nicotine patches versus 9% given placebo. Other studies have found varied benefit.

CONTRAINDICATIONS AND PRECAUTIONS

Contraindications:
- Hypersensitivity
- Recent cerebrovascular event, severe arrhythmia, recent myocardial infarction, unstable angina, uncontrolled hypertension (causes coronary and peripheral vasoconstriction, tachycardia)
- Broken skin (patches)
- Concurrent use of tobacco products (risk of excessive nicotine; discontinue replacement product if unable to stop smoking and set a new quit date; for exceptions see DOSAGE)
- Pregnancy (see PREGNANCY AND LACTATION)
- Temperomandibular joint disease (gum)
- Children
- Nonsmokers
- MRI (patch must be removed before MRI; aluminum in the patch can cause burns)

Precautions
- Less severe cardiovascular disease, stable angina, hypertension, peripheral vascular disease, hypertension (caution, possible tachycardia, and coronary and peripheral vasoconstriction, see SIDE EFFECTS)
- Endocrine disorders: pheochromocytoma, hyperthyroidism, insulin-dependent diabetes mellitus (caution, release of catecholamines from adrenal medulla)
- Peptic ulcer disease (caution, delays healing)
- Severe renal impairment (caution, reduced elimination)
- Lactation (see PREGNANCY AND LACTATION)
- Hepatic impairment (caution, reduced metabolism)
- Asthma and COPD (inhaler may irritate respiratory tract, use another dosage form)
- Dental appliances and fillings (gum may stick)
- Pre-existing oral/pharyngeal/esophageal irritation (gum may exacerbate)
- Phenylketonuria: Nicorette mint flavour lozenges contain aspartame, which is converted to phenylalanine
- Strenuous exercise: Patch absorption may increase; remove patch before exercise
- Myasthenia gravis (possible exacerbation; these patients have a reduced number of nicotinic ACh receptors at the neuromuscular junction)
- Ingestion of small amounts may be toxic, even fatal, to children and pets: keep out of their reach
- Report any unexpected or serious reactions to Health Canada's adverse reaction monitoring program (toll free telephone 1-866-234-2345, toll free fax 1-866-678-6789).

PREGNANCY AND LACTATION
Smoking during pregnancy carries clear risks of low birth weight, increased risk of spontaneous abortion and increased perinatal mortality. It is not clear how much of this toxicity is due to nicotine and how much to the many other chemicals produced by smoking. Theoretically, smoking with its multiple toxins is more hazardous in pregnancy than exposure to nicotine alone although one study has suggested the contrary.

In some animals, high-dose nicotine has been shown to be teratogenic (neurotoxicity, skeletal defects, limb deformities, cleft palate), decrease fetal body weight, and to increase stillbirths. In monkeys, nicotine decreases uterine blood flow.

In human pregnancies, the toxicity of nicotine replacement therapy is controversial. Nicotine clearance is increased in pregnant women, and the fetus has a higher nicotine serum level than the mother. Some studies of nicotine replacement report small changes in fetal blood pressure and heart rate that are usually less pronounced than those caused by smoking, a case of arrhythmia, loss of fetal heart rate reactivity, increased risk of congenital defects, and rare cases of miscarriage, while other studies report safe use of nicotine in pregnancy with no reduction in birth weight. Nicotine withdrawal in the fetus is possible: increased fetal movement was reported in one case when smoking was replaced by nicotine; this resolved when smoking was resumed.

Several studies suggest that nicotine replacement is ineffective in pregnancy. Since pregnant women metabolize nicotine faster than non-pregnant women, higher doses may be required for it to be effective in this population, although there is no direct evidence and this raises safety considerations.

Conclusion: Nicotine use in pregnancy is contraindicated by many authorities. A pregnant woman who smokes should be encouraged to stop smoking without using nicotine replacement. Some authorities note that if non-drug techniques to stop smoking are not successful, the known risks of continuing to smoke should be weighed against the unknown risks and benefits of nicotine replacement therapy, with every attempt made to reduce nicotine exposure, e.g. low doses, intermittent exposure, removal of nicotine patches at night.

Ideally, smoking should be avoided while breast feeding since it reduces milk production and infant weight gain. There are no data on the toxicity of nicotine in breast milk. Nicotine is distributed into breast milk with a milk:plasma ratio of 2.9 and it is absorbed orally. In one study, infant doses of nicotine from smoking, 21 mg patches, 14 mg patches and 7 mg patches were 5.8, 4.9, 3.6 and 2.2 micrograms/kg/day respectively. Since the risks are unknown, nicotine replacement therapy could be considered if non-drug measures fail. Reduce exposure to nicotine by using intermittent dosing, removing patches at night, and breastfeeding when nicotine levels would be lowest, e.g. 2-3 hours after chewing the gum.

SIDE EFFECTS

All dosage forms can produce similar types of systemic nicotinic adverse effects as well as local irritation (oropharyngeal for the gum, less oral irritation with the lozenge, mostly oropharyngeal with some respiratory irritation with the inhaler, or dermal irritation at the site of patch application). In smoking cessation, an attempt should be made to differentiate symptoms of nicotine withdrawal (irritability, anxiety, trouble sleeping, nervousness, depressed mood, difficulty concentrating, restlessness, increased appetite and headaches) from the adverse effects of nicotine (dizziness, rash, sweating, abdominal pain, insomnia, palpitations). Most side effects and withdrawal symptoms sometimes improve over a few days or can be eliminated by adjusting the dose of the nicotine replacement product. Incidence is indicated in brackets.

Cardiovascular: Chest pain (gum, lozenge 1%), increased blood pressure (all dosage forms), palpitations (gum 5%), tachycardia (patch 1.2% versus 0.3% with placebo). Case reports of myocardial infarction, notably in patients who smoke while using a patch, and stroke; however, studies find no increase in cardiovascular risk compared with stopping smoking without nicotine replacement.
CNS: Headache (mild, gum 11%, inhaler 26% vs. 15% with placebo, lozenge 8% vs. 3% with placebo); dizziness (gum 19%, patch); insomnia (gum, lozenge, patch); abnormal dreams (patch 5.7% vs. 1.4% with placebo); seizures with high doses.
Dermatologic: Transient itching/burning/tingling/redness (patch 8.6% vs. 1.4% with placebo).
Endocrine/Metabolic: Increased insulin levels and insulin resistance (gum).
Gastrointestinal: Nausea (gum 20-40%, lozenge 12-15% vs. 5% with placebo, patch 8%); dyspepsia (gum 9%, inhaler 18% vs. 9% with placebo, lozenge, patch 6% vs. 3% with placebo); mouth and throat irritation/soreness/ulceration (gum 4-60%, inhaler 40%, lozenge 7%, patch 2.6% vs. 1.2% with placebo; heartburn (lozenge 5% vs. 1-2% with placebo); altered taste (gum 4%, inhaler at least 3%, lozenge); injury to teeth or dental work (gum 2%, stickier and harder than ordinary gum); increased salivation (gum, initially); hiccups (due to excessive swallowing of nicotine, gum 15-22%, reduce chewing, lozenge 3-8% vs. placebo 0%); belching (gum, from swallowing air while chewing, change chewing technique, lozenge 1%); decreased lower esophageal sphincter pressure; tongue discolouration/ulceration.
Hypersensitivity: Persistent skin irritation (patch), local swelling (patch).

Neuromuscular: Mild jaw muscle ache (gum, 18-45%); pain in jaws and neck (inhaler at least 3%), myalgia (patch 7% vs. 0% with placebo); paresthesias; exacerbation of myasthenia gravis (these patients have a reduced number of nicotinic ACh receptors at the neuromuscular junction).
Respiratory: Cough (gum 1%, inhaler 32% vs. 12% with placebo), lozenge (5% vs. 3% with placebo), patch 3% vs. 1% with placebo, upper respiratory tract infection (lozenge 10-12% vs. 6-10% with placebo).
Other: Weight gain (all dosage forms similar and not different from placebo, 2-6kg versus 4-5kg with placebo). Dependence (20-25% continue to use gum for more than 1 year; potential may be higher with gum/lozenge/inhaler due to higher rapid nicotine levels). Hot flashes.

INTERACTIONS
Nicotine is a substrate of CYP 2A6. The polycyclic hydrocarbons from smoking tobacco induce CYP1A2; thus when a patient, especially a moderate to heavy smoker, stops smoking, de-induction of CYP1A2 can lead to increased levels of drugs that are metabolized by this enzyme. Both nicotine and smoking increase catecholamine levels, thus catecholamine levels may drop when a patient stops smoking and the dosage of adrenergic agonists and adrenergic antagonists may require adjustment (see below).

DRUG	EFFECT	MECHANISM	IMPORTANCE
Adrenergic agonists (isoproterenol, phenylephrine)	Decreased adrenergic effect	Relatively lower catecholamine levels when smoking stops	Caution, increase dose of adrenergic agonist
Adrenergic antagonists (prazosin, labetalol)	Increased adrenergic antagonist effect	Relatively lower catecholamine levels when smoking stops	Caution, decrease dose of adrenergic antagonist
Alcohol	Intensified effect of alcohol	Unknown	Caution
Caffeine	Increased caffeine levels	Decreased metabolism (de-induction of CYP1A2 when smoking stops)	Reduction of caffeine intake may be necessary
Cimetidine	Increased nicotine levels	Decreased metabolism	Caution, monitor
Clozapine	Increased clozapine levels	Decreased metabolism (de-induction of CYP1A2 when smoking stops)	Reduction of clozapine dose may be necessary
Drugs partly metabolized by CYP1A2*****	Increased drug levels	Decreased metabolism (de-induction of CYP1A2 when smoking stops)	Reduction of drug dose may be necessary

Insulin	Increased insulin level	Increased sc absorption when smoking stops	Caution, adjust dose
Methoxsalen	Increased nicotine levels	Decreased metabolism (CYP2A6)	Caution
Oral contraceptives (estrogen-progestin)	Decreased nicotine levels	Increased metabolism	Caution
Ranitidine	Increased nicotine levels	Decreased metabolism	Caution, monitor
Theophylline	Increased theophylline levels	Decreased metabolism (de-induction of CYP1A2 when smoking stops)	Reduction of theophylline dose may be necessary
Vasopressin	Myocardial ischemia	Increased afterload and coronary artery vasoconstriction	Remove patch 24 hours before surgery

***** Drugs partly metabolized by CYP1A2 include: Acetaminophen, clomipramine, fluvoxamine, imipramine, propranolol, olanzapine.

Interactions are lacking with:
Bupropion

DOSAGE
Smokers should stop smoking completely as they start nicotine replacement therapy, unless they are using the gum occasionally to help them through non-smoking situations, or using the "reduce-to-quit" strategy described below.

Adults:
Gum: The 4mg gum is used by patients who smoke more than 20-25 cigarettes daily or who score 7 or greater on the Fagerstrom Scale.

- ***Abrupt quit***: One piece of gum is chewed over a 30 minute period when there is a craving to smoke. Commonly, a one-pack-a-day smoker chews once per hour initially. Maximum one piece per hour, 20 pieces per day, usually for 3 months. Do not discontinue suddenly; at three months, the dose is gradually reduced, for example every 4-7 days. The patient can stop when a dose of 1-2 pieces per day is reached.
- ***Reduce-to-quit gradual reduction***: Substitute one piece of gum for cigarettes when there is an urge to smoke. Try to reduce cigarette smoking by 50% between 6 weeks and 4 months. Continue until smoking has completely ceased; then follow directions for an "abrupt quit". Maximum 20 pieces/day, maximum 12 months.

Inhaler: Patients may self-titrate to the dose required to reduce abstinence symptoms, generally 6-12 cartridges per day for up to 3 months. Follow by a gradual weaning period over 12 weeks with discontinuation when 1-2 cartridges per day are used. Duration of treatment should not exceed 6 months.
Lozenge: Oral: Initially 1 lozenge every 1-2 hours, dissolved in the mouth, for the first 6 weeks. Then 1 lozenge every 2-4 hours for 3 weeks, followed by 1 lozenge every 4-8 hours for 3 weeks. Lozenges can then be used as needed for a further 3 months. Maximum 15 lozenges per day, maximum 6 months. Use the 4mg lozenge if the first cigarette is smoked within 30 minutes of waking up.

Patch: ***Dermal:***

- ***Patients without cardiovascular disease, weight over 45kg (100 pounds) or smoking more than 10 cigarettes per day***: One 21mg/day patch once daily for 6 weeks. Reassess initial dose based on response in the first two weeks. Discontinue regimen if not successful at 4 weeks. Otherwise, switch to one 14mg/day patch once daily for 2 weeks, then one 7mg/day patch once daily for 2 weeks.
- ***Patients with cardiovascular disease, weight under 45kg (100 pounds) or smoking less than 10 cigarettes per day***: One 14mg/day patch once daily for 6 weeks. Reassess initial dose based on response in the first two weeks. Discontinue regimen if not successful at 4 weeks. Otherwise, switch to one 7mg/day patch once daily for 2 weeks. Maximum 12 weeks.

Elderly: As for adults.

Children: Use is not recommended by manufacturers, but may be considered in adolescents although efficacy is not clear. Adult dosing of patches and gum for 12 weeks was safe in 13-17 year olds in one study.

Hepatic and renal impairment: Dosage adjustments are not required.

NURSING IMPLICATIONS

Patch: Check for allergies to adhesives prior to application. Change once daily. Monitor application sites for swelling or erythema that persist more than 1 day. If these occur switch to a different route.

Gum, lozenges and inhaler: Can be used regularly around the clock or as needed for cravings. Avoid eating and drinking liquids, especially acidic beverages (coffee, tea, soft drinks, alcohol, citrus juices), 15 minutes before administration.

Ensure that a tapering schedule is in place for all dosage forms. If patches are used for over 3 months or inhalers and gums for over 3-6 months, the duration should be questioned and dependence should be assessed.

For common side effects and what to do if they occur, see PATIENT INSTRUCTIONS below.

Signs of nicotine toxicity may occur in the following order: nausea/vomiting, drooling, abdominal pain, diarrhea, pale skin, cold sweat, severe headache, dizziness, disturbed hearing/vision, tremor, confusion, weakness, extreme exhaustion, fainting, low blood pressure, difficulty breathing, fast/weak/irregular heart beat, and seizures. Additional dangerous side effects: chest pain, irregular heartbeat, palpitations, leg pain or a persistent stomach upset. Withhold drug should any of the above symptoms appear and notify physician immediately. N.B. because some nicotine is left in the skin when you take a patch off, the nicotine will continue to pass into the bloodstream for several hours after patch removal.

Short-term therapeutic benefits in smoking cessation include decreased cravings for tobacco products and prevention of nicotine withdrawal symptoms such as irritability, insomnia, increased appetite, anxiety, restlessness, and headaches. Long-term benefits include smoking cessation and prevention of smoking-related illnesses.

For instructions on the use of nicotine gum, inhalers, lozenges, or transdermal patches, see Patient Instructions below.

PATIENT INSTRUCTIONS

Nicotine chewing gum, inhalers, lozenges and transdermal patches are used to help people stop smoking cigarettes. They provide a source of nicotine that reduces withdrawal symptoms experienced when smoking is stopped and are sometimes called "nicotine replacement therapy" or NRT.

Before using this medication, talk to your physician or pharmacist if you have any allergies, medical conditions, are pregnant or breastfeeding, plan to become pregnant, or if you are taking any medications.

Ask your physician or pharmacist to help you select the right product and dosing regimen based on your smoking habits, preferences and medical history. Smoking cessation programs are available to help you. Ask your physician or pharmacist for resources.

It is essential that you stop smoking when you are using nicotine replacement therapy to quit smoking. Otherwise, you are in danger of receiving too much nicotine. Exceptions include patients who are using a gradual reduction method (reduce-to-quit), or in temporary situations when smoking is not permitted.

In general, regimens for smoking cessation last from 3-6 months. The dose of nicotine must be gradually tapered over time. Patches are not appropriate for occasional smokers.

Side effects:
Nausea, headaches (mild), lightheadedness, sweating, insomnia, stomach upset and vivid dreams can be caused by excess nicotine. Irritability, trouble sleeping, nervousness, increased appetite and headaches can be caused by nicotine withdrawal. These side effects and withdrawal symptoms sometimes improve over a few days or can be eliminated by adjusting the dose of the nicotine replacement product.
If you experience chest pain, irregular heartbeat, palpitations, leg pain or a persistent stomach upset while using a nicotine product, stop using the product and consult your physician.

All nicotine products should be stored in their original packaging away from heat, light and moisture, and out of the reach of children and animals. Used gum, inhaler cartridges and patches contain enough nicotine to seriously harm a child or pet.

If a child comes in contact with any nicotine product, consult your physician or local poison control centre right away. If you have experienced any unexpected or serious reaction to this drug, this can be reported to Health Canada's monitoring program (toll free telephone 1-866-234-2345, toll free fax 1-866-678-6789). Note that this is not an emergency number.

Instructions for specific dosage forms
Gum:
- Carry the gum with you at all times.
- Do not eat or drink, especially coffee, tea, fruit juice, or soft drinks, for 15 minutes before chewing a piece of gum.
- Nicotine gum should not be chewed like regular gum and should not be swallowed. Each piece must be chewed SLOWLY and intermittently over 30 minutes; if you chew too fast you may feel light-headed or nauseous. Belching may be due to swallowing air; change chewing technique. Hiccups may occur if excessive nicotine is swallowed; chew less vigorously. Chew only one piece of gum at a time.
- Take one piece of gum and bite into the gum slowly once or twice until you taste the nicotine or feel a slight tingling in your mouth.
- Then park it between your cheek and gum and keep it there until the tingling is almost gone, allowing nicotine to be released.
-Repeat. Slow down if you start feeling uncomfortable. After about 30 minutes, you will have released all the medication.
-Do not exceed 20 pieces per day or more than one piece per hour. As you reduce your dosage, possibly by one piece per day every 4-7 days, you can substitute sugarless gum or candy for the nicotine gum.
-Consult your dentist or physician if injury or irritation to the mouth, jaw, teeth or dental work occurs.

Inhaler:
- Carry the inhaler and cartridges with you at all times.
- Use at room temperature; inhaling at cold temperatures releases less nicotine.
- Avoid acidic drinks including coffee, tea, soft drinks and fruit juice since these may reduce nicotine absorption.
- Puff on the inhaler as needed. Each cartridge provides up to 20 minutes of puffing, but you may wish to puff for a few minutes at a time. Initially, continuous puffing for 20 minutes is recommended. Clean the mouthpiece regularly.
- Many people experience mild irritation of the mouth or throat, and cough when they first use the inhaler. These side effects decrease with continued use.

Lozenge:
- Carry the lozenges with you at all times.

- Wait 15 minutes after eating or drinking, and do not eat or drink while the lozenge is in your mouth. Dissolve one lozenge in the mouth slowly over 20-30 minutes, moving the lozenge from one side of the mouth to the other with your tongue until it is completely dissolved. Do not chew or swallow the lozenge.

Transdermal patch:
- Remove the old patch and place it folded in half, sticky side inward in a protective pouch for safe disposal. Adhesive residue may be removed with rubbing alcohol.
- Apply a new patch to healthy, clean, dry and non-hairy skin on the outer area of your upper arm or on your back or front above the waist, avoiding breasts for women. Vary site of application each day and do not use a site more than once per week.
- Press firmly for at least 10 seconds with the heel of your hand and ensure that the edges are sticking well.
- Try to do this at the same time everyday to help you remember to change your patch.
- Wash hands after application.
- It is normal to experience mild itching, burning or tingling when you first apply a patch, but this should disappear within an hour. If skin irritation persists, if redness lasts more than one day or if swelling occurs, do not apply another patch and call your healthcare professional.
- If you are having unusual dreams or disturbed sleep, take the patch off before going to bed and put a new one on in the morning.
- Bathing, showering, and swimming for short periods will not usually affect the patch if it is applied correctly. If a patch does fall off, apply a new one.
- To avoid symptoms of nicotine overdose do not smoke while using a patch, do not use more than one patch at a time, and remove your patch 2 hours before engaging in prolonged, strenuous exercise or scuba diving.
- Do not cut or trim patches.

PRESENTATION
Gum: Delivers 2, 4mg. Available in various flavours (fresh mint, ice mint, fresh fruit).
Lozenge: Delivers 2, 4mg.
Inhaler: Delivers 4mg.
Transdermal patch: Delivers 7, 14, 21 mg/day.

References are available on request.

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