Appendix A6.1.5.5 Summary Safety of FDA-approved Pharmacotherapies

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LIST OF ABBREVIATIONS

AE	adverse event
ARCI	Addiction Research Center Inventories
AUC	area under curve
BID	twice daily
CI	confidence interval
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
COSTART	Coding Symbols for a Thesaurus of Adverse Reaction Terms
C-SSRS	Columbia-Suicide Severity Rating Scale
CVA	cerebrovascular accident
FDA	US Food and Drug Administration
HLGT	high level group terms (MedDRA)
HR	hazard ratio
LD50	median lethal dose
LVOTO	left ventricular outflow tract obstruction
MACE	major adverse cardiovascular events
MAO	monoamine oxidase
MAOI	monoamine oxidase inhibitor
MDD	major depressive disorder
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MRHD	maximum recommended human dose
NBDPS	National Birth Defects Prevention Study

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NRT	nicotine replacement therapy
NS	nasal spray
NTS	nicotine transdermal system
OR	odds ratio
OTC	over-the-counter
PT	preferred terms (MedDRA)
PVD	peripheral vascular disease
RR	risk ratio
VSD	ventricular septal defect

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1 INTRODUCTION

Smoking is the leading preventable cause of illness and premature death worldwide. Some medications have been proven to help people to quit, with three licensed for this purpose in Europe and the USA: nicotine replacement therapy (NRT), bupropion, and varenicline. Bupropion, varenicline and several types of NRT are widely available on prescription, whereas some other types of NRT are over-the-counter (OTC) medications. They are licensed as first-line treatments for use as smoking cessation aids in the USA and the European Union.

The objective of this review is to evaluate the safety profile of the US Food and Drug Administration (FDA)-approved smoking cessation pharmacotherapies. To that purpose, this report comprises a compilation of the safety information included in the current FDA-approved labels for the corresponding pharmacotherapies. Consumers can consult a FDA health information document on smoking cessation products (FDA 101: Smoking Cessation Products), which provides general information as well as recommendations and precautions on the usage of these products.

2 SAFETY INFORMATION

2.1 Nicotine Replacement Therapy

2.1.1 Overview of the Nicotine Replacement Therapy Types

2.1.1.1 Nicotine Nasal Spray

Nicotine nasal spray (NS) delivers nicotine faster than the other NRTs by directly delivering it to the nasal cavity. The dose of nasal spray varies depending on the individual level of dependence and severity of symptom. Individuals who use nasal spray are more than twice as likely to have long-term abstinence from cigarette smoking as compared with placebo treatment. Nasal spray may cause nasal burning, itching, and irritation, and adherence rates tend to be lower than those for other forms of NRTs (Herman 2010).

2.1.1.2 Nicotine Inhaler

The nicotine inhaler contains a vaporized cartridge of nicotine placed in a plastic container with the mouthpiece similar to that used in the treatment of asthma. The user should either inhale deeply into the back of the throat or puff in short breaths. Most of the nicotine is absorbed through the buccal mucosa rather than through the lungs, as in smoking. However, puffs are highly variable and dependent on factors such as consistency of delivery between puffs as well as air temperature. The nicotine inhaler can cause local irritation, such as a burning sensation in the throat, coughing, sneezing, dizziness, nausea, and indigestion. These side effects may compromise compliance with heavy use and may reduce the efficacy of an inhaler (Herman 2010).

2.1.1.3 Nicotine Patch

The nicotine patch delivers nicotine transdermally at a relatively steady rate. The steady state nicotine levels with patch treatment are about half those obtained through smoking.

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The nicotine patch is currently available in 24-hour delivery system on the US market. The 24-hour delivery system is available in 7, 14, or 21 mg doses.

The advantages of the nicotine patch include ease of administration, few side effects (skin irritation, nausea, vomiting, sweating, mood and sleep disturbances), and once-daily dosing, all of which may lead to better compliance. Nicotine patches, however, do not seem to be effective against craving episodes (Herman 2010).

2.1.1.4 Nicotine Gum

Nicotine polacrilex gum is available OTC in 2 or 4 mg doses. With nicotine gum administration, nicotine is absorbed through buccal mucosa, reaching peak plasma nicotine concentrations within 15 to 30 minutes, as compared with 1 to 2 minutes after smoking. The main side effects of gum include nausea, burping, hiccups, and jaw fatigue. Acidic beverages such as coffee and juices should be avoided before and after the use of nicotine gum because they decrease the absorption of nicotine (Herman 2010).

2.1.1.5 Nicotine Lozenge

Similar to nicotine gum, the lozenge is available OTC in 2 or 4 mg doses of nicotine. Compared with the same dose of nicotine gum, the lozenge delivers about 25% more nicotine, as some nicotine is retained in the gum, and the lozenge is dissolved completely. Nicotine lozenges may be particularly well-suited for smokers who wear dentures, have temporomandibular joint pain, or prefer not to chew gum (Herman 2010).

2.1.2 Nicotine Replacement Therapy with a Prescription Status: Nicotrol Nasal Spray and Nicotrol Inhaler

All of the information below has been derived from the Nicotrol NS (nicotine nasal spray) label information and the Nicotrol inhaler (nicotine inhalation system) label information.

2.1.2.1 Indications and Usage

Nicotrol NS and Nicotrol Inhaler are indicated as aids to smoking cessation for the relief of nicotine withdrawal symptoms. This medication should be used/is recommended as a part of a comprehensive behavioral smoking cessation program.

The safety and efficacy of the continued use for periods longer than 6 months have not been adequately studied and such use is not recommended.

2.1.2.2 Contraindications

Use of Nicotrol NS and Inhaler therapy is contraindicated in patients with known hypersensitivity or allergy to nicotine or to any component of the product (including menthol for the Inhaler).

2.1.2.3 Warnings and Precautions

2.1.2.3.1 Warnings

Nicotine from any source can be toxic and addictive. Smoking causes lung disease, cancer, and heart disease and may adversely affect pregnant women or the fetus.

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For any smoker, with or without concomitant disease or pregnancy, the risk of nicotine replacement in a smoking cessation program should be weighed against the hazard of continued smoking, and the likelihood of achieving cessation of smoking without nicotine replacement.

Pregnancy

Tobacco smoke, which has been shown to be harmful to the fetus, contains nicotine, hydrogen cyanide, and carbon monoxide. The Nicotrol Inhaler does not deliver hydrogen cyanide and carbon monoxide. Nicotine has been shown in animal studies to cause fetal harm. It is therefore presumed that Nicotrol NS and Nicotrol Inhaler can cause fetal harm when administered to a pregnant woman.

The effect of nicotine delivery by Nicotrol NS and Nicotrol Inhaler has not been examined during pregnancy. Therefore, pregnant smokers should be encouraged to attempt cessation using educational and behavioral interventions before using pharmacological approaches.

If Nicotrol NS or Nicotrol Inhaler is used during pregnancy, or if the patient becomes pregnant while using it, the patient should be apprised of the potential hazard to the fetus.

Safety note concerning children

The amounts of nicotine that are tolerated by adult smokers can produce symptoms of poisoning and could prove fatal if Nicotrol NS is used or ingested, or if the Inhaler is inhaled, ingested, or buccally absorbed by children or pets. A full bottle of Nicotrol NS contains 100 mg of nicotine, some of which will still be in the bottle when it is discarded. One cartridge of Nicotrol Inhaler initially contains 10 mg nicotine, and contains about 60% of its initial drug content when it is discarded, which is about 6 mg. Therefore, patients should be cautioned to keep both used and unused containers or cartridges of Nicotrol NS or Inhaler respectively out of the reach of children and pets. All components of the Nicotrol Inhaler system should also be kept out of the reach of children and pets to avoid accidental swallowing and choking.

2.1.2.3.2 Precautions

General

The patient should be urged to stop smoking completely when initiating Nicotrol NS or Inhaler therapy. Patients should be informed that if they continue to smoke while using the product, 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 treatment should be discontinued. Physicians should anticipate that concomitant medications may need dosage adjustment.

Use of Nicotrol NS is not recommended in patients with known chronic nasal disorders (e.g. allergy, rhinitis, nasal polyps and sinusitis) since such use has not been adequately studied.

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Asthma, bronchospasm and reactive airway disease

Nicotine is an airway irritant and might cause bronchospasm.

Exacerbation of bronchospasm in patients with pre-existing asthma has been reported with Nicotrol NS. Use of Nicotrol NS in patients with severe reactive airway disease is not recommended.

Nicotrol Inhaler has not been specifically studied in asthma or chronic pulmonary disease. Nicotrol Inhaler should be used with caution in patients with bronchospastic disease. Other forms of nicotine replacement might be preferable in patients with severe bronchospastic airway disease.

Effect of Nicotrol NS on the nasal mucosa

Topical application of either nicotine or tobacco products is irritating to the nasal mucosa and physicians should consider both the risks and benefits to the patient before initiating or continuing Nicotrol NS therapy.

The effect of Nicotrol NS on the nasal mucosa was studied in 39 cigarette smokers who used Nicotrol NS for 1 month. When compared to baseline, random biopsies taken after four weeks of treatment revealed 1 patient with persistence of pre-existing dysplasia and 1 patient with a newly found dysplasia. In both, dysplasia was not seen after a recovery period of eight weeks.

Forty-two patients who used Nicotrol NS for more than 6 months underwent follow-up ear, nose and throat examinations 1 to 3 months after discontinuing the use of the spray. Many reported local irritant effects of the spray during spray use, but none showed persistent mucosal injury that the examining physician could attribute to use of the product. The clinical significance of these findings is not known, but extended use of the product beyond six months is not recommended.

Cardiovascular or peripheral vascular diseases

The risks of nicotine replacement in patients with 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 [MI] and/or angina pectoris), serious cardiac arrhythmias, or vasospastic diseases (Buerger's disease, Prinzmetal's variant angina and Raynaud's phenomena) should be evaluated carefully before nicotine replacement is prescribed.

Tachycardia and palpitations have been reported occasionally with the use of Nicotrol Inhaler as well as with other nicotine replacement therapies. No serious cardiovascular events were reported in clinical studies with Nicotrol Inhaler and NS, but if symptoms occur, its use should be discontinued.

Nicotrol NS and Inhaler should generally not be used in patients during the immediate post-MI period, nor in patients with serious arrhythmias, or with severe or worsening angina.

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Renal or hepatic insufficiency

The pharmacokinetics of nicotine have not been studied in the elderly or in patients with renal or 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. Only severe renal impairment would be expected to affect the clearance of nicotine or its metabolites from the circulation.

Endocrine diseases

Nicotrol NS and Inhaler 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.

Peptic ulcer disease

Nicotine delays healing in peptic ulcer disease; therefore, Nicotrol NS and Inhaler 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 outweigh the risks.

Accelerated hypertension

Nicotine therapy constitutes a risk factor for development of malignant hypertension in patients with accelerated hypertension; therefore, Nicotrol NS and Inhaler therapy should be used with caution in these patients and only when the benefits of including nicotine replacement in a smoking cessation program outweigh the risks.

Information for patient

A patient instruction sheet is included in the package of Nicotrol NS and Inhaler cartridges dispensed to the patient. Patients should be encouraged to read the instruction sheet carefully and to ask their physician and pharmacist about the proper use of the product.

It should be explained to patients that they are likely to experience nasal irritation using Nicotrol NS, which may become less bothersome with continued use.

Carcinogenesis, mutagenesis and impairment of fertility

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 forestomach 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. Neither nicotine nor cotinine was mutagenic in the Ames salmonella test. Nicotine induced reparable DNA damage in an *E. coli* test system.

Nicotine was shown to be genotoxic in a test system using Chinese hamster ovary cells. 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.

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2.1.2.4 Adverse Reactions

2.1.2.4.1 Nicotrol Nasal Spray

Assessment of adverse events (AEs) in the 730 patients who participated in controlled clinical trials is complicated by the occurrence of signs and symptoms of nicotine withdrawal in some patients and nicotine excess in others. The incidence of AEs is confounded by the many minor complaints that smokers commonly have, by continued smoking by many patients and the local irritation from both active drug and the pepper placebo. No serious AEs were reported during the trials.

Common smoker's complaints

Common complaints experienced by the smokers in the study (users of both active and placebo spray) include: chest tightness, dyspepsia, paraesthesia (tingling) in limbs, constipation, and stomatitis.

Tobacco withdrawal symptoms

Symptoms of tobacco withdrawal were frequent in users of both active and placebo sprays. Common withdrawal symptoms seen in over 5% of patients included: anxiety, irritability, restlessness, cravings, dizziness, impaired concentration, weight increase, emotional lability, somnolence and fatigue, increased sweating, and insomnia. Less frequently seen probable withdrawal symptoms (under 5%) included: confusion, depression, apathy, tremor, increased appetite, incoordination and increased dreaming. Anxiety, irritability, restlessness and tobacco cravings occurred about equally in both groups, while other symptoms tended to be slightly more common on placebo spray.

Effects of the spray

Nicotrol NS and the pepper-containing placebo were both associated with irritant side effects on the nasopharyngeal and ocular tissues. During the first 2 days of treatment, nasal irritation was reported by nearly all (94%) of the patients, the majority of whom rated it as either moderate or severe. Both the frequency and severity of nasal irritation declined with continued use of Nicotrol NS but was still experienced by most (81%) of the patients after 3 weeks of treatment, with most patients rating it as moderate or mild. Other common side-effects for both active and placebo groups were: runny nose, throat irritation, watering eyes, sneezing, and coughing. The following local events were reported somewhat more commonly for active than for placebo spray: nasal congestion, subjective comments related to the taste or use of the dosage form, sinus irritation, transient epistaxis, eye irritation, transient changes in sense of smell, pharyngitis, paraethesias of the nose, mouth or head, numbness of the nose, or mouth, burning of the nose or eyes, earache, facial flushing, transient changes in sense of taste, hoarseness, nasal ulcer or blister.

Nicotine-related adverse events

Feelings of dependence on the spray were reported by more patients on active spray than placebo. Drug-like effects such as calming were also more frequent on active spray.

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Other adverse events

AEs which could not be classified and listed above and which were reported by > 1% of patients on active spray are listed in Table 1:

Table 1 Adverse Events not Attributable to Intercurrent Illness

Adverse Event (%)	Active (N=369)	Placebo (N=361)
Headache	18	15
Back pain	6	4
Dyspnea	5	6
Nausea	5	5
Arthralgia	5	1
Menstrual disorder	4	4
Palpitation	4	4
Flatulence	4	3
Tooth disorder	4	1
Gum problems	4	1
Myalgia	3	4
Abdominal pain	3	3
Confusion	3	3
Acne	3	1
Dysmenorrheal	3	0
Pruritus	2	3

AEs reported with a frequency of < 1% among active spray users are listed below:

- Body as a Whole: edema peripheral, pain, numbness, allergy.
- Gastrointestinal: dry mouth, hiccup, diarrhea.
- Hematologic: purpura.
- Neurological: aphasia, amnesia, migraine, numbness.
- Respiratory: bronchitis, bronchospasm, sputum increased.
- Skin and Appendages: rash, purpura.
- Special Senses: vision abnormal.

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2.1.2.4.2 Nicotrol Inhaler

Assessment of AEs in the 1,439 patients (730 on active drug) who participated in controlled clinical trials (including three dose finding studies) is complicated by the occurrence of signs and symptoms of nicotine withdrawal in some patients and nicotine excess in others. The incidence of AEs is confounded by: (1) the many minor complaints that smokers commonly have, (2) continued smoking by many patients and (3) the local irritation from both the active drug and the placebo.

Common smoker's complaints

Smoking related AEs present in > 3% of patients on active drug include chest discomfort, bronchitis, and hypertension.

Tobacco withdrawal symptoms

Symptoms of withdrawal were common in both active and placebo groups. Common withdrawal symptoms seen in > 3% of patients on active drug included: dizziness, anxiety, sleep disorder, depression, withdrawal syndrome, drug dependence, fatigue and myalgia.

Effects of the inhaler

Nicotrol Inhaler and the placebo were both associated with local irritant side effects. Local irritation in mouth and throat was reported by 40% of patients on active drug as compared to 18% of patients on placebo. Irritant effects were higher in the two pivotal trials with higher doses being 66% on active drug and 42% on placebo. Coughing (32% active versus 12% placebo) and rhinitis (23% active versus 16% placebo) were also higher on active drug. The majority of patients rated these symptoms as mild. The frequency of cough, and mouth and throat irritation declined with continued use of Nicotrol Inhaler. Other AEs that occurred in > 3% of patients on active drug in placebo controlled pivotal trials considered possibly related to the local irritant effects of the Nicotrol Inhaler are taste comments, pain in jaw and neck, tooth disorders and sinusitis.

Nicotine-related adverse events

The most common nicotine-related AE was dyspepsia. This was present in 18% of patients in the active group compared to 9% of patients in the placebo group. Other nicotine-related events present in > 3% of patients on active drug include nausea, diarrhea, and hiccup.

Other adverse events

AEs of unknown relationship to nicotine occurring in > 3% of patients on active drug include headache (26% of patients on active and 15% of patients on placebo), influenza-like symptoms, pain, back-pain, allergy, paresthesias, flatulence and fever.

2.1.2.5 Drug Interactions

For Nicotrol NS the extent of absorption and peak plasma concentration is slightly reduced in patients with the common cold/rhinitis. In addition, the time to peak concentration is prolonged. The use of a nasal vasoconstrictor in patients with rhinitis will further prolong the time to peak.

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Smoking cessation, with or without nicotine replacement, may alter the pharmacokinetics of certain concomitant medications such as tricyclic antidepressants and theophylline. Doses of these and perhaps other medications that may need to be adjusted in patients who successfully quit smoking are described in Table 2.

Table 2 Overview of Medications Which may Require a Decrease in Dose at Cessation of Smoking

May Require a Decrease in Dose at Cessation of Smoking	**Possible Mechanism**
Acetaminophen, caffeine, imipramine, oxazepam, pentazocine, propranolol, or other beta-blockers, theophylline	De-induction of hepatic enzymes on smoking cessation.
Insulin	Increase of subcutaneous insulin absorption with smoking cessation.
Adrenergic antagonists (e.g. prazosin, labetalol)	Decrease in circulating catecholamines with smoking cessation.
May Require an Increase in Dose at Cessation of Smoking	**Possible Mechanism**
Adrenergic agonists (e.g. isoproterenol, phenylephrine)	Decrease in circulating catecholamines with smoking cessation.

2.1.2.6 Use in Specific Populations

2.1.2.6.1 Pregnancy

The following applies to Category D pregnancy (see FDA Pregnancy Categories), indicating that there is positive evidence of human fetal risk based on adverse reaction data from either investigational or marketing experience, or from studies in humans. However, potential benefits may warrant use of the drug in pregnant women despite potential risks.

The harmful effects of cigarette smoking on maternal and fetal health are clearly established. These include low birth weight, an increased risk of spontaneous abortion, and increased perinatal mortality. The specific effects of Nicotrol NS and Inhaler on fetal development are unknown. Therefore pregnant smokers should be encouraged to attempt cessation using educational and behavioral interventions before using pharmacological approaches.

Spontaneous abortion during nicotine replacement therapy has been reported; as with smoking, nicotine as a contributing factor cannot be excluded.

Nicotrol NS and Inhaler should be used during pregnancy only if the likelihood of smoking cessation justifies the potential risk of using it by the pregnant patient, who might continue to smoke.

Teratogenicity

Animal Studies: Nicotine was shown to produce skeletal abnormalities in the offspring of mice when toxic doses were given to the dams (25 mg/kg intraperitoneal or subcutaneous).

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Human Studies: 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.

Other effects

Animal Studies: A nicotine bolus (up to 2 mg/kg) to pregnant rhesus monkeys caused acidosis, hypercarbia, and hypotension (fetal and maternal concentrations were about 20 times those achieved after smoking one cigarette in 5 minutes). Fetal breathing movements were reduced in the fetal lamb after intravenous injection of 0.25 mg/kg nicotine to the ewe (equivalent to smoking 1 cigarette every 20 seconds for 5 minutes). Uterine blood flow was reduced about 30% after infusion of 0.1 µg/kg/min nicotine to pregnant rhesus monkeys (equivalent to smoking about six cigarettes every minute for 20 minutes).

Human Experience: Cigarette smoking during pregnancy is associated with an increased risk of spontaneous abortion, low birth weight infants and perinatal mortality. Nicotine and carbon monoxide are considered the most likely mediators of these outcomes. The effects of cigarette smoking on fetal cardiovascular parameters have been studied near term. Cigarettes increased fetal aortic blood flow and heart rate and decreased uterine blood flow and fetal breathing movements. Nicotrol NS and Inhaler have not been studied in pregnant women.

Labor and delivery

Nicotrol NS and Inhaler are not recommended for use during labor and delivery. The effect of nicotine on a mother or the fetus during labor is unknown.

2.1.2.6.2 Use in Nursing Mothers

Caution should be exercised when Nicotrol NS or Inhaler is administered to nursing mothers. The safety of Nicotrol NS and Inhaler 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. An infant has the ability to clear nicotine by hepatic first-pass clearance; however, the efficiency of removal is probably lowest at birth. Nicotine concentrations in milk can be expected to be lower with Nicotrol NS and Inhaler when used as recommended than with cigarette smoking, as maternal plasma nicotine concentrations are generally reduced with nicotine replacement. The risk of exposure of the infant to nicotine from Nicotrol NS and Inhaler therapy should be weighed against the risks associated with the infant's exposure to nicotine from continued smoking by the mother (passive smoke exposure and contamination of breast milk with other components of tobacco smoke) and from Nicotrol NS and Inhaler alone, or in combination with continued smoking.

2.1.2.6.3 Pediatric Use

Safety and effectiveness in pediatric and adolescent patients below the age of 18 years have not been established for any nicotine replacement product. However, no specific medical risk is known or expected in nicotine dependent adolescents. Nicotrol Inhaler should be used for the treatment of tobacco dependence in the older adolescent only if the

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potential benefit justifies the potential risk. Nicotrol NS therapy is not recommended for use in pediatric population because its safety and effectiveness in children and adolescents who smoke have not been evaluated.

2.1.2.6.4 Geriatric Use

Clinical studies of Nicotrol NS and Inhaler did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reports on clinical experience have not identified differences between older and younger patients. In general, dosage selection for an elderly patient should be cautious, usually starting at the low end of the dosage range reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease.

2.1.2.7 Drug Abuse and Dependence

2.1.2.7.1 Nicotrol Nasal Spray

Nicotrol NS has a dependence potential intermediate between other nicotine-based therapies and cigarettes. This is the result of differences between cigarettes, Nicotrol NS, nicotine gum and nicotine patches in pharmacokinetic and dosing characteristics commonly associated with abuse and dependence. Nicotrol NS is distinct from other nicotine-based smoking cessation therapies in its greater speed of onset, greater capacity for self-titration of dose, and frequent and rapid fluctuations in plasma nicotine concentration.

Dependence on nicotine NS occurred in the clinical trials. Feelings of dependency on the spray were reported by 32% of active spray users and 13% of placebo spray users.

Such dependence may represent transference of tobacco-related nicotine dependence to Nicotrol NS.

2.1.2.7.2 Nicotrol Inhaler

Nicotrol Inhaler is likely to have a low abuse potential based on differences between the product and cigarettes in three characteristics commonly considered important in contributing to abuse: slower absorption, smaller fluctuations in blood levels and lower blood levels of nicotine. Nicotrol Inhaler, like many other nicotine-based smoking cessation therapies, does not produce arterial concentrations similar to cigarettes. However, nicotine withdrawal symptoms were noted in clinical trials at the time of Nicotrol Inhaler tapering and after Nicotrol Inhaler discontinuation.

Dependence might occur from transference of tobacco-related nicotine dependence to the Nicotrol Inhaler. The use of the inhaler beyond 6 months has not been evaluated in clinical trials and is not recommended. To minimize the risk of dependence, patients should be encouraged to withdraw gradually from Nicotrol Inhaler therapy after 3 months of usage. If necessary, dose reduction can be achieved by gradual reduction of the dose over a 6 to 12 week period.

2.1.2.8 Overdosage

The oral median lethal dose (LD50) for nicotine is > 5 mg/kg in dogs and > 24 mg/kg in rodents. Death is due to respiratory paralysis. The oral minimum acute lethal dose for

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nicotine in adult humans is reported to be 40 to 60 mg (< 1 mg/kg). A full bottle of Nicotrol NS contains 100 mg of nicotine. One cartridge of Nicotrol Inhaler contains 10 mg nicotine, of which, approximately 4 mg is delivered.

Nicotrol NS would be expected to be irritating if sprayed in the eyes, mouth or ears. Eye exposure should be treated with copious irrigation with water for 20 minutes.

The effects of using several cartridges in rapid succession are unknown. It is unlikely that an excessive nicotine overdose will occur via inhalation. Should such an overdose occur, however, with signs of nicotine poisoning, the patient should be instructed to contact his/her physician immediately and to call for additional emergency information, the regional poison center or the National Capital Poison Center toll free (1-800-222-1222).

Signs and symptoms of nicotine toxicity

Signs and symptoms of an overdose of Nicotrol NS or Inhaler would be 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 produce convulsions quickly and death follows as a result of peripheral or central respiratory paralysis or, less frequently, cardiac failure.

Overdosis from ingestion

Large oral nicotine ingestions cause vomiting, and the consequences of an overdose will vary; should this occur, patients should contact their physician immediately and for additional emergency information, they should call the regional poison center or National Capital Poison center.

Nicotrol NS: If emesis has not occurred, it should be induced in conscious patients with a suitable emetic followed by an appropriate dose of activated charcoal. In unconscious patients with a secure airway, instill activated charcoal via a nasogastric tube. A saline cathartic or sorbitol may be added to the first dose of activated charcoal.

Nicotrol Inhaler: Persons ingesting Nicotrol Inhaler cartridges should be referred to a health care facility for management. In unconscious patients with a secure airway, instill activated charcoal via a nasogastric tube. A saline cathartic or sorbitol may be added to the first dose of activated charcoal. Repeated doses of activated charcoal should be administered as long as the cartridge remains in the gastrointestinal tract since it will continue to release nicotine for many hours. The Nicotrol Inhaler cartridges can be identified with a radiogram.

Management of nicotine poisoning for Nicotrol NS and Nicotrol Inhaler

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.

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2.1.3 Nicotine Replacement Therapies with Over-the-Counter Status: Gums, Lozenges and Transdermal Systems

2.1.3.1 General Safety Information in the Product Labeling (Drug Facts) of Over-the-Counter Nicotine Replacement Therapies Available on the US Market

The information below has been derived from the FDA-approved labels for the following medicines: Nicorette (nicotine polacrilex lozenge), Nicorette (nicotine polacrilex gum), Nicotine polacrilex Gum USP, Nicoderm CQ (nicotine transdermal system) and Habitrol (nicotine transdermal system).

2.1.3.1.1 Purpose

Stop smoking aid.

2.1.3.1.2 Use

To reduce withdrawal symptoms, including nicotine craving, associated with quitting smoking.

2.1.3.1.3 Warnings

If you are pregnant or breast-feeding, only use this medicine on the advice of your health care provider.

Smoking can seriously harm your child. Try to stop smoking without using any nicotine replacement medicine. This medicine is believed to be safer than smoking. However the risks to your child from this medicine are believed to be safer than smoking.

Do not use if you:

- are allergic for soya (only for mint flavor Lozenge)
- continue to smoke, chew tobacco, use snuff, or use a nicotine patch or other nicotine containing products (This contra-indication is only mentioned for some Nicotine polacrilex Gums)

Ask a doctor before use if you have:

- heart disease, recent heart attack, or irregular heartbeat. Nicotine can increase your heart rate.
- high blood pressure not controlled with medication. Nicotine can increase your blood pressure.
- stomach ulcer or diabetes when using gums, or lozenge
- a sodium-restricted diet when using some gums or lozenge
- history of seizures when using some gums or lozenge
- diabetes when using some patches
- an allergy to adhesive tape or have skin problems because you are more likely to get rashes when using patches.

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Ask a doctor or pharmacist before use if you are:

- using a non-nicotine stop smoking drug
- taking prescription medicine for depression or asthma. Your prescription dose may need to be adjusted

When using patches:

If you have vivid dreams or other sleep disturbances remove this patch at bedtime. Do not smoke, even when not wearing the patch. The nicotine in your skin will still be entering your bloodstream for several hours after you take off the patch.

Stop use and ask a doctor if:

- irregular heartbeat or palpitations occur
- symptoms of nicotine overdose such as nausea, vomiting, dizziness, weakness, rapid heartbeat occur
- mouth problems occur (for lozenge and gums only)
- teeth or jaw problems occur (for gums only)
- persistent indigestion or severe throat occurs (for lozenge only)
- skin redness caused by patch does not go away after four days, or if your skin swells or you get a rash (for patches only)
- symptoms of an allergic reaction (such as difficulty breathing or rash in case of use of lozenge and some gums or patches) occur
- oral blistering occurs (for cinnamon surge gum only)

Keep out of reach of children and pets.

Used patches, nicotine lozenges and gum have enough nicotine to poison children and pets. Dispose of the used patches by folding sticky ends together. Replace in pouch and discard. To remove the lozenge or pieces of gum, wrap it in paper and throw away in the trash. In case of overdose, get medical help or contact a Poison Control Center right away.

2.1.3.1.4 Directions

If you are under 18 years of age, ask a doctor before use. Being used on your quit day.

In case of patches, do not leave them on for more than 24 hours because it may irritate your skin and loses strength after 24 hours.

In case of lozenge and gum, do not use more than one at a time or continuously use one after another since this may cause you hiccups, heartburn, nausea or other side effects.

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2.1.3.2 Additional Safety Information in the User's Guide of Over-the-Counter Nicotine Replacement Therapies Available on the US Market

The information provided below has been retrieved from the user's guides that are available on the FDA website for nicotine transdermal patches, lozenges and gums (Drugs@FDA: FDA Approved Drug Products). An overview is given of precautions, warnings and possible side effects associated with the usage of these NRTs.

2.1.3.2.1 Nicotine Transdermal Patches

Nicotine related symptoms

The NRTs do not contain tar or carbon monoxide of cigarette smoke, and do not have the same medical dangers as tobacco. However, the nicotine transdermal system (NTS) still delivers nicotine, the addictive part of cigarette smoke. Nicotine can cause unpleasant effects such as headache, nausea, dizziness and upset stomach.

Skin reactions

The patch may cause a skin reaction at the application site.

Following advice is given in the user's guide: If your skin reacts to the Nicotine Transdermal patches when you first put on a patch, mild itching, burning, or tingling at the patch application site is normal and should go away within an hour. After you remove a patch, the skin under the patch might be somewhat red. Your skin should not stay red for more than a day after removing the patch. If you have a skin rash or redness caused by the patch that does not go away after 4 days, or your skin swells, call your doctor. Do not put on a new patch; you may be allergic to one of the components of the patch.

Skin discoloration is also mentioned among the skin side effects.

Nicotine withdrawal symptoms

Following advice is given in user's guide:

You'll need to prepare yourself for some nicotine withdrawal symptoms. These begin almost immediately after you stop smoking, and are usually at their worst during the first three or four days. Understand that any of the following is possible:

- craving for nicotine
- anxiety, irritability, restlessness, mood changes, nervousness
- disruptions of your sleep
- drowsiness
- trouble concentrating
- increased appetite and weight gain
- headaches, muscular pain, constipation,
- fatigue

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The patch reduces nicotine withdrawal symptoms such as irritability and nervousness, as well as the craving for nicotine you used to satisfy by having a cigarette.

These typical nicotine withdrawal symptoms will go away with time. Your smoker's cough will get worse before it gets better. Coughing helps clear the tar deposits out of your lungs.

Overdose symptoms

Signs of an overdose would include pallor (extreme paleness), cold sweat, nausea, abnormal salivation, vomiting, abdominal pain or severe headache, disturbed hearing or vision, dizziness, mental confusion or weakness.

Other side effects mentioned in the user's guide:

- Irregular hearbeats or palpitations
- Severe chest pain or tightening
- Diarrhea
- Dry mouth
- Vivid dreams

2.1.3.2.2 Lozenge and Gums

The nicotine related symptoms and withdrawal symptoms mentioned above are also detailed for lozenge and gums.

Lozenges can cause mouth or throat irritation, headache and hiccups.

Because nicotine polacrilex gum is a gum-based product, chewing it can cause dental fillings to loosen or aggravate other mouth and jaw problems. Nicotine polacrilex gums can also cause hiccups, heartburn and other stomach problems, especially if chewed too quickly or not chewed correctly.

2.2 Varenicline (Chantix)

Varenicline, is a selective nicotinic receptor partial agonist, licensed as a prescription-only treatment for smoking cessation by the FDA in 2006. In smokers, varenicline attenuates the subjective rewarding responses and heart rate increases induced by intravenous nicotine. Varenicline also improves tobacco withdrawal symptoms, mood, and cognitive performance in abstinent smokers. All these effects may contribute to varenicline's efficacy for smoking cessation (Cahill 2013, Herman 2010).

Unless indicated otherwise, all of the information below has been derived from the FDA-approved Full Prescribing Information for CHANTIX (varenicline) Tablets.

2.2.1 Indications and Usage

Chantix is indicated for use as an aid to smoking cessation treatment. The standard regimen of varenicline is 1 mg twice a day for 12 weeks, with the first week titrated to reduce side effects, and quit date set for the second week (Cahill 2013).

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2.2.2 Contraindications

Chantix is contraindicated in patients with a known history of serious hypersensitivity reactions or skin reactions to Chantix.

2.2.3 Warnings and Precautions

2.2.3.1 Neuropsychiatric Symptoms and Suicidality

Serious neuropsychiatric symptoms have been reported in patients being treated with Chantix. These post-marketing reports have included changes in mood (including depression and mania), psychosis, hallucinations, paranoia, delusions, homicidal ideation, hostility, agitation, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed suicide. Some reported cases may have been complicated by the symptoms of nicotine withdrawal in patients who stopped smoking. Depressed mood may be a symptom of nicotine withdrawal. Depression, rarely including suicidal ideation, has been reported in smokers undergoing a smoking cessation attempt without medication. However, some of these symptoms have occurred in patients taking Chantix who continued to smoke. When symptoms were reported, most were during Chantix treatment, but some were following discontinuation of Chantix therapy. These events have occurred in patients with and without pre-existing psychiatric disease; some patients have experienced worsening of their psychiatric illnesses. All patients being treated with Chantix should be observed for neuropsychiatric symptoms or worsening of pre-existing psychiatric illness. Patients with serious psychiatric illness such as schizophrenia, bipolar disorder, and major depressive disorder (MDD) did not participate in the pre-marketing studies of Chantix. Limited safety data are available from post-marketing smoking cessation studies in two patient groups: 1) patients with MDD, and 2) patients with stable schizophrenia or schizoaffective disorder.

Some reported neuropsychiatric events, including unusual and sometimes aggressive behavior directed to oneself or others, may have been worsened by concomitant use of alcohol.

Patients and caregivers should be advised that the patient should stop taking Chantix and that a healthcare provider should be contacted immediately if agitation, depressed mood, changes in behavior or thinking that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behavior. In many post-marketing cases, resolution of symptoms after discontinuation of Chantix was reported, although in some cases the symptoms persisted, therefore, ongoing monitoring and supportive care should be provided until symptoms resolve.

The risks of Chantix should be weighed against the benefits of its use. Chantix has been demonstrated to increase the likelihood of abstinence from smoking for as long as one year compared to treatment with placebo. The health benefits of quitting smoking are immediate and substantial.

Since the initial signal of neuropsychiatric symptoms and suicidality emerged, additional analyses and studies have been conducted to further evaluate this association.

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Analyses of Clinical Trials

A meta-analysis of 5 randomized, double-blind, placebo controlled trials, including 1907 patients (1130 Chantix, 777 placebo) was conducted to assess suicidal ideation and behavior as reported on the Columbia-Suicide Severity Rating Scale (C-SSRS). This meta-analysis included one trial (N=127) in patients with a history of schizophrenia or schizoaffective disorder and another trial (N=525) in patients with a history of depression. The results showed no increase in the incidence of suicidal ideation and/or behavior in patients treated with Chantix compared to patients treated with placebo, with a Risk Ratio (RR) of 0.79 (95% Confidence Interval [CI]: 0.46, 1.36), as shown in Table 3. Forty-eight (48) of the 55 patients who reported suicidal ideation or behavior (24 Chantix, 24 placebo) were observed in the two trials that enrolled patients with a history of schizophrenia, schizoaffective disorder, or depression. Few events were observed in the other three trials (4 Chantix, 3 placebo).

Table 3 Number of Patients and Risk Ratio for Suicidal Ideation and/or Behavior Reported on C-SSRS from a Meta-Analysis of 5 Clinical Trials Comparing Chantix to Placebo

	Chantix (N=1130)	Placebo (N=777)
Patients with suicidal ideation and/or behavior* [n (%)]**	28 (2.5)	27 (3.5)
Patient-years of exposure	325	217
Risk Ratio # (RR; 95% CI)	0.79 (0.46, 1.36)	

* Of the events, one patient in each treatment arm reported suicidal behavior
** Patients with events up to 30 days after treatment; % are not weighted by study
# RR: incidence rates per 100 patient years

A pooled analysis of 18 double-blind, randomized, placebo-controlled clinical trials, which includes the 5 trials that collected C-SSRS described in Table 3, was conducted to assess the psychiatric safety of Chantix. This pooled analysis included 8521 patients (5072 Chantix, 3449 placebo), some of whom had psychiatric conditions at baseline. Table 4 describes the most frequently (≥ 1%) reported AEs related to psychiatric safety. The results showed a similar incidence of common psychiatric events in patients treated with Chantix compared to patients treated with placebo.

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Table 4 Psychiatric Adverse Events Occurring in ≥ 1% of Patients from Pooled Analysis of 18 Clinical Trials

n (%)	Chantix (N=5072)	Placebo (N=3449)
Anxiety disorders and symptoms	253 (5.0)	206 (6.0)
Depressed mood disorders and disturbances	179 (3.5)	108 (3.1)
Mood disorders and disturbances NEC*	116 (2.3)	53 (1.5)

* NEC = Not Elsewhere Classified
Counts (percentages) correspond to the number of patients reporting the event

Observational Studies

Four observational studies, each including 10,000 to 30,000 users of Chantix in the adjusted analyses, compared the risk of selected serious neuropsychiatric events (neuropsychiatric hospitalizations, fatal and non-fatal self-harm), between Chantix users and prescription NRT or bupropion users.

All studies were retrospective cohort studies and included patients with and without a psychiatric history.

Two of the studies found no difference in risk of neuropsychiatric hospitalizations between Chantix users and nicotine patch users (Hazard Ratio [HR] 1.14; 95% CI: 0.56–2.34 in the first study, and 0.76; 95% CI: 0.40-1.46 in the second study). However, neither study validated the diagnostic codes used to identify outcomes against medical records. A third study reported no difference in risk of psychiatric AEs diagnosed during an emergency department visit or inpatient admission between Chantix users and bupropion users (HR 0.85; 95% CI: 0.55-1.30). Bupropion has also been associated with neuropsychiatric AEs. A fourth study examined risk of fatal and non-fatal self-harm in users of Chantix compared to users of NRT. Although the occurrence of detected suicide was rare during the three months after patients initiated any drug treatment (two cases in 31,260 Chantix users and six cases in 81,545 NRT users), this study has important limitations. Most importantly, these data were captured following public awareness of reports of neuropsychiatric AEs in Chantix users. Chantix users had fewer comorbid conditions that could put them at risk for neuropsychiatric AEs, suggesting that patients with a history of neuropsychiatric illness were preferentially prescribed NRT, and healthier patients were preferentially prescribed Chantix.

Outcomes examined in these studies did not include the full range of neuropsychiatric AEs that have been reported.

2.2.3.2 Seizures

During clinical trials and the post-marketing experience, there have been reports of seizures in patients treated with Chantix. Some patients had no history of seizures, whereas others had a history of seizure disorder that was remote or well-controlled. In

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most cases, the seizure occurred within the first month of therapy. This potential risk should be weighed against the potential benefits before prescribing Chantix in patients with a history of seizures or other factors that can lower the seizure threshold. Patients should be advised to discontinue Chantix and contact a healthcare provider immediately if they experience a seizure while on treatment.

2.2.3.3 Interaction with Alcohol

There have been post-marketing reports of patients experiencing increased intoxicating effects of alcohol while taking Chantix. Some cases described unusual and sometimes aggressive behavior, and were often accompanied by amnesia for the events. Patients should be advised to reduce the amount of alcohol they consume while taking Chantix until they know whether Chantix affects their tolerance for alcohol.

2.2.3.4 Accidental Injury

There have been post-marketing reports of traffic accidents, near-miss incidents in traffic, or other accidental injuries in patients taking Chantix. In some cases, the patients reported somnolence, dizziness, loss of consciousness or difficulty concentrating that resulted in impairment, or concern about potential impairment, in driving or operating machinery. Patients should be advised to use caution driving or operating machinery or engaging in other potentially hazardous activities until they know how Chantix may affect them.

2.2.3.5 Cardiovascular Events

In a placebo-controlled clinical trial of Chantix administered to patients with stable cardiovascular disease, with approximately 350 patients per treatment arm, all-cause and cardiovascular mortality was lower in patients treated with Chantix, but certain non-fatal cardiovascular events occurred more frequently in patients treated with Chantix than in patients treated with placebo. Table 5 shows the incidence of deaths and of selected non-fatal serious cardiovascular events occurring more frequently in the Chantix arm compared to the placebo arm. These events were adjudicated by an independent blinded committee. Non-fatal serious cardiovascular events not listed occurred at the same incidence or more commonly in the placebo arm. Patients with more than one cardiovascular event of the same type are counted only once per row. Some of the patients requiring coronary revascularization underwent the procedure as part of management of non-fatal MI and hospitalization for angina.

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Table 5 Mortality and Adjudicated Non-Fatal Serious Cardiovascular Events in the Placebo-Controlled Chantix Trial in Patients with Stable Cardiovascular Disease

Mortality and Cardiovascular Events, n (%)	Chantix (N=353)	Placebo (N=350)
Mortality (cardiovascular and all-cause up to 52 weeks)		
Cardiovascular death	1 (0.3)	2 (0.6)
All-cause mortality	2 (0.6)	5 (1.4)
Non-fatal cardiovascular events (rate on Chantix > Placebo)		
Up to 30 days after treatment		
Non-fatal myocardial infarction	4 (1.1)	1 (0.6)
Non-fatal stroke	2 (0.6)	0 (0)
Beyond 30 days after treatment and up to 52 weeks		
Non-fatal myocardial infarction	3 (0.8)	2 (0.6)
Need for coronary revascularization	7 (2.0)	2 (0.6)
Hospitalization for angina pectoris	6 (1.7)	4 (1.1)
Transient ischemia attack	1 (0.3)	0 (0)
New diagnosis of PVD or admission for a PVD procedure	5 (1.4)	2 (0.6)

A meta-analysis of 15 clinical trials of ≥ 12 weeks treatment duration, including 7002 patients (4190 Chantix, 2812 placebo), was conducted to systematically assess the cardiovascular safety of Chantix. The study in patients with stable cardiovascular disease described above was included in the meta-analysis. There were lower rates of all-cause mortality (Chantix 6 [0.14%]; placebo 7 [0.25%]) and cardiovascular mortality (Chantix 2 [0.05%]; placebo 2 [0.07%]) in the Chantix arms compared with the placebo arms in the meta-analysis.

The key cardiovascular safety analysis included occurrence and timing of a composite endpoint of Major Adverse Cardiovascular Events (MACE), defined as cardiovascular death, non-fatal MI, and non-fatal stroke. These events included in the endpoint were adjudicated by a blinded, independent committee. Overall, a small number of MACE occurred in the trials included in the meta-analysis, as described in Table 6. These events occurred primarily in patients with known cardiovascular disease.

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Table 6 Number of MACE cases, Hazard Ratio and Rate Difference in a Meta-Analysis of 15 Clinical Trials Comparing Chantix to Placebo*

	Chantix (N=4190)	Placebo (N=2812)
MACE cases [n (%)]	13 (0.31)	6 (0.21)
Patient-years of exposure	1316	839
Hazard ratio (95% CI)	1.95 (0.79, 4.82)	
Rate difference per 1000 patient-years (95% CI)	6.30 (-2.40, 15.10)	

* Includes MACE occurring up to 30 days post-treatment

The meta-analysis showed that exposure to Chantix resulted in a HR for MACE of 1.95 (95% CI from 0.79 to 4.82) for patients up to 30 days after treatment; this is equivalent to an estimated increase of 6.3 MACE events per 1000 patient-years of exposure. The meta-analysis showed higher rates of cardiovascular endpoints in patients on Chantix relative to placebo across different time frames and pre-specified sensitivity analyses, including various study groupings and cardiovascular outcomes. Although these findings were not statistically significant they were consistent. Because the number of events was small overall, the power for finding a statistically significant difference in a signal of this magnitude is low.

Chantix was not studied in patients with unstable cardiovascular disease or cardiovascular events occurring within two months before screening. Patients should be advised to notify a health care provider of new or worsening symptoms of cardiovascular disease. The risks of Chantix should be weighed against the benefits of its use in smokers with cardiovascular disease. Smoking is an independent and major risk factor for cardiovascular disease. Chantix has been demonstrated to increase the likelihood of abstinence from smoking for as long as one year compared to treatment with placebo.

2.2.3.6 Angioedema and Hypersensitivity Reactions

There have been post-marketing reports of hypersensitivity reactions including angioedema in patients treated with Chantix. Clinical signs included swelling of the face, mouth (tongue, lips, and gums), extremities, and neck (throat and larynx). There were infrequent reports of life-threatening angioedema requiring emergent medical attention due to respiratory compromise. Patients should be instructed to discontinue Chantix and to seek medical care immediately if they experience these symptoms.

2.2.3.7 Serious Skin Reactions

There have been post-marketing reports of rare but serious skin reactions, including Stevens-Johnson Syndrome and erythema multiforme, in patients using Chantix. As these skin reactions can be life-threatening, patients should be instructed to stop taking Chantix and contact a healthcare provider immediately at the first appearance of a skin rash with mucosal lesions or any other signs of hypersensitivity.

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2.2.3.8 Nausea

Nausea was the most common adverse reaction reported with Chantix treatment. Nausea was generally described as mild or moderate and often transient; however, for some patients, it was persistent over several months. The incidence of nausea was dose-dependent. Initial dose-titration was beneficial in reducing the occurrence of nausea. For patients treated to the maximum recommended dose of 1 mg twice daily following initial dosage titration, the incidence of nausea was 30% compared with 10% in patients taking a comparable placebo regimen. In patients taking Chantix 0.5 mg twice daily following initial titration, the incidence was 16% compared with 11% for placebo. Approximately 3% of patients treated with Chantix 1 mg twice daily in studies involving 12 weeks of treatment discontinued treatment prematurely because of nausea. For patients with intolerable nausea, a dose reduction should be considered.

2.2.4 Adverse Reactions

The following serious adverse reactions were reported in post-marketing experience and are discussed in greater detail in Section 2.2.3:

- Neuropsychiatric symptoms and suicidality
- Seizures
- Interaction with Alcohol
- Accidental injury
- Cardiovascular Events
- Angioedema and hypersensitivity reactions
- Serious skin reactions

In the placebo-controlled pre-marketing studies, the most common AEs associated with Chantix (> 5% and twice the rate seen in placebo-treated patients) were nausea, abnormal (vivid, unusual, or strange) dreams, constipation, flatulence, and vomiting.

The treatment discontinuation rate due to AEs in patients dosed with 1 mg twice daily was 12% for Chantix, compared to 10% for placebo in studies of three months' treatment. In this group, the discontinuation rates that are higher than placebo for the most common AEs in Chantix-treated patients were as follows: nausea (3% vs. 0.5% for placebo), insomnia (1.2% vs. 1.1% for placebo), and abnormal dreams (0.3% vs. 0.2% for placebo).

Smoking cessation, with or without treatment, is associated with nicotine withdrawal symptoms and has also been associated with the exacerbation of underlying psychiatric illness.

2.2.4.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, the adverse reactions rates observed in the clinical studies of a drug cannot be directly compared to

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rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

During the pre-marketing development of Chantix, over 4500 subjects were exposed to Chantix, with over 450 treated for at least 24 weeks and approximately 100 for a year. Most study participants were treated for 12 weeks or less.

The most common AE associated with Chantix treatment is nausea, occurring in 30% of patients treated at the recommended dose, compared with 10% in patients taking a comparable placebo regimen.

Table 7 shows the AEs for Chantix and placebo in the 12 week fixed dose pre-marketing studies with titration in the first week. AEs were categorized using the Medical Dictionary for Regulatory Activities (MedDRA, Version 7.1).

MedDRA High Level Group Terms (HLGT) reported in ≥ 5% of patients in the Chantix 1 mg twice daily (BID) dose group, and more commonly than in the placebo group, are listed, along with subordinate Preferred Terms (PT) reported in ≥ 1% of Chantix patients (and at least 0.5% more frequent than placebo). Closely related PTs such as 'Insomnia', 'Initial insomnia', 'Middle insomnia', 'Early morning awakening' were grouped, but individual patients reporting two or more grouped events are only counted once.

Table 7 Common Treatment-Emergent AEs (%) in the Fixed-Dose, Placebo-Controlled Studies (HLGTs > 5% of Patients in the 1 mg BID Chantix Group and More Commonly Than Placebo and PT ≥ 1% in the 1 mg BID Chantix Group, and 1 mg BID Chantix at Least 0.5% More Than Placebo)

System Organ Class High Level Group Term Preferred Term	Chantix 0.5 mg BID (N=129)	Chantix 1 mg BID (N=821)	Placebo (N=805)
Gastrointestinal Signs and Symptoms			
Nausea	16	30	10
Abdominal Pain *	5	7	5
Flatulence	9	6	3
Dyspepsia	5	5	3
Vomiting	1	5	2
GI Motility/Defecation Conditions			
Constipation	5	8	3
Gastroesophageal reflux disease	1	1	0
Salivary Gland Conditions			
Dry mouth	4	6	4
Psychiatric Disorders			

table continues

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System Organ Class High Level Group Term Preferred Term	Chantix 0.5 mg BID (N=129)	Chantix 1 mg BID (N=821)	Placebo (N=805)
Sleep Disorder/Disturbances			
Insomnia **	19	18	13
Abnormal dreams	9	13	5
Sleep disorder	2	5	3
Nightmare	2	1	0
Nervous System			
Headaches			
Headache	19	15	13
Neurological Disorders NEC #			
Dysgeusia	8	5	4
Somnolence	3	3	2
Lethargy	2	1	0
General Disorders			
General Disorders NEC #			
Fatigue/Malaise/Asthenia	4	7	6
Respiriratory/Thoracic/Mediastinal Disorders			
Respiratory Disorders NEC #			
Rhinorrhea	0	1	0
Dyspnea	2	1	1
Upper Respiratory Tract Disorder	7	5	4
Skin/Subcutaneous Tissue			
Epidermal and Dermal Conditions			
Rash	1	3	2
Pruritis	0	1	1
Metabolism & Nutrition			
Appetite/General Nutritional Disorders			
Increased appetite	4	3	2
Decreased appetite/ Anorexia	1	2	1

* Includes PTs Abdominal (pain, pain upper, pain lower, discomfort, tenderness, distension) and Stomach discomfort

** Includes PTs Insomnia/Initial insomnia/Middle insomnia/Early morning awakening

NEC = Not Elsewhere Classified

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The overall pattern and frequency of AEs during the longer-term pre-marketing trials was similar to those described in Table 7, though several of the most common events were reported by a greater proportion of patients with long-term use (e.g., nausea was reported in 40% of patients treated with Chantix 1 mg twice daily in a one-year study, compared to 8% of placebo-treated patients).

Following is a list of treatment-emergent AEs reported by patients treated with Chantix during all pre-marketing clinical trials and updated based on pooled data from 18 placebo-controlled pre- and post-marketing studies, including approximately 5,000 patients treated with varenicline. AEs were categorized using MedDRA, Version 16.0. The listing does not include those events already listed in the previous tables or elsewhere in this report, those events for which a drug cause was remote, those events which were so general as to be uninformative, and those events reported only once which did not have a substantial probability of being acutely life-threatening.

- Blood and Lymphatic System Disorders. *Infrequent:* anemia, lymphadenopathy. *Rare:* leukocytosis, splenomegaly, thrombocytopenia.
- Cardiac Disorders. *Infrequent:* angina pectoris, MI, palpitations, tachycardia. *Rare:* acute coronary syndrome, arrhythmia, atrial fibrillation, bradycardia, cardiac flutter, cor pulmonale, coronary artery disease, ventricular extrasystoles.
- Ear and Labyrinth Disorders. *Infrequent:* tinnitus, vertigo. *Rare:* deafness, Meniere's disease.
- Endocrine Disorders. *Infrequent:* thyroid gland disorders.
- Eye Disorders. *Infrequent:* conjunctivitis, eye irritation, eye pain, vision blurred, visual impairment. *Rare:* blindness transient, cataract subcapsular, dry eye, night blindness, ocular vascular disorder, photophobia, vitreous floaters.
- Gastrointestinal Disorders. *Frequent:* diarrhea, toothache. *Infrequent:* dysphagia, eructation, gastritis, gastrointestinal hemorrhage, mouth ulceration. *Rare:* enterocolitis, esophagitis, gastric ulcer, intestinal obstruction, pancreatitis acute.
- General Disorders and Administration Site Conditions. *Frequent:* chest pain. *Infrequent:* chest discomfort, chills, edema, influenza-like illness, pyrexia.
- Hepatobiliary Disorders. *Rare:* gall bladder disorder.
- Investigations. *Frequent:* liver function test abnormal, weight increased. *Infrequent:* electrocardiogram abnormal. *Rare:* muscle enzyme increased, urine analysis abnormal.
- Metabolism and Nutrition Disorders. *Infrequent:* diabetes mellitus, hypoglycemia. *Rare:* hyperlipidemia, hypokalemia.
- Musculoskeletal and Connective Tissue Disorders. *Frequent:* arthralgia, back pain, myalgia. *Infrequent:* arthritis, muscle cramp, musculoskeletal pain. *Rare:* myositis, osteoporosis.

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- Nervous System Disorders. *Frequent:* disturbance in attention, dizziness. *Infrequent:* amnesia, convulsion, migraine, parosmia, syncope, tremor. *Rare:* balance disorder, cerebrovascular accident (CVA), dysarthria, mental impairment, multiple sclerosis, VIIth nerve paralysis, nystagmus, psychomotor hyperactivity, psychomotor skills impaired, restless legs syndrome, sensory disturbance, transient ischemic attack, visual field defect.
- Psychiatric Disorders. *Infrequent:* dissociation, libido decreased, mood swings, thinking abnormal. *Rare:* bradyphrenia, disorientation, euphoric mood.
- Renal and Urinary Disorders. *Infrequent:* nocturia, pollakiuria, urine abnormality. *Rare:* nephrolithiasis, polyuria, renal failure acute, urethral syndrome, urinary retention.
- Reproductive System and Breast Disorders. *Frequent:* menstrual disorder. *Infrequent:* erectile dysfunction. *Rare:* sexual dysfunction.
- Respiratory, Thoracic and Mediastinal Disorders. *Frequent:* respiratory disorders. *Infrequent:* asthma, epistaxis, rhinitis allergic, upper respiratory tract inflammation. *Rare:* pleurisy, pulmonary embolism.
- Skin and Subcutaneous Tissue Disorders. *Infrequent:* acne, dry skin, eczema, erythema, hyperhidrosis, urticaria. *Rare:* photosensitivity reaction, psoriasis.
- Vascular Disorders. *Infrequent:* hot flush. *Rare:* thrombosis.

Chantix has also been studied in post-marketing trials including (1) a trial conducted in patients with chronic obstructive pulmonary disease (COPD), (2) a trial conducted in generally healthy patients (similar to those in the pre-marketing studies) in which it was allowed to select a quit date between days 8 and 35 of treatment ("alternative quit date instruction trial"), (3) a trial conducted in patients who did not succeed in stopping smoking during prior Chantix therapy, or who relapsed after treatment ("re-treatment trial"), (4) a trial conducted in patients with stable cardiovascular disease, (5) a trial conducted in patients with stable schizophrenia or schizoaffective disorder and (6) a trial conducted in patients with MDD.

AEs in the trial of patients with COPD, in the alternative quit date instruction trial, were quantitatively and qualitatively similar to those observed in pre-marketing studies. In the re-treatment trial, the profile of common AEs was similar to that previously reported, but, in addition, varenicline-treated patients also commonly reported diarrhea (6% vs 4% in placebo-treated patients), depressed mood disorders and disturbances (6% vs 1%), and other mood disorders and disturbances (5% vs 2%).

In the trial of patients with stable cardiovascular disease, more types and a greater number of cardiovascular events were reported compared to pre-marketing studies. Treatment-emergent (on-treatment or 30 days after treatment) cardiovascular events reported with a frequency ≥ 1% in either treatment group in this study were angina pectoris (3.7% and 2.0% for varenicline and placebo, respectively), chest pain (2.5% vs. 2.3%), peripheral edema (2.0% vs. 1.1%), hypertension (1.4% vs. 2.6%), and palpitations (0.6 % vs. 1.1%). Deaths and serious cardiovascular events occurring over the 52 weeks

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of the study (treatment emergent and non-treatment emergent) were adjudicated by a blinded, independent committee. The following treatment-emergent adjudicated events occurred with a frequency > 1% in either treatment group: non-fatal MI (1.1% vs. 0.3% for varenicline and placebo, respectively), and hospitalization for angina pectoris (0.6% vs. 1.1%). During non-treatment follow up to 52 weeks, the adjudicated events included need for coronary revascularization (2.0% vs. 0.6%), hospitalization for angina pectoris (1.7% vs. 1.1%), and new diagnosis of peripheral vascular disease (PVD) or admission for a PVD procedure (1.4% vs. 0.6%). Some of the patients requiring coronary revascularization underwent the procedure as part of management of non-fatal MI and hospitalization for angina. Cardiovascular death occurred in 0.3% of the patients in the varenicline arm and 0.6% of patients in the placebo arm over the course of the 52-week study.

In the trial of patients with stable schizophrenia or schizoaffective disorder, 128 smokers on antipsychotic medication were randomized 2:1 to varenicline (1 mg twice daily) or placebo for 12 weeks with 12-week non-drug follow-up. The most common AEs in patients taking varenicline were nausea (24% vs. 14.0% on placebo), headache (11% vs. 19% on placebo) and vomiting (11% vs. 9% on placebo). Among reported neuropsychiatric AEs, insomnia was the only event that occurred in either treatment group in ≥ 5% of subjects at a rate higher in the varenicline group than in placebo (10% vs. 5%). These common and neuropsychiatric AEs occurred on treatment or within 30 days after the last dose of study drug. There was no consistent worsening of schizophrenia in either treatment group as measured by the Positive and Negative Syndrome Scale. There were no overall changes in extra-pyramidal signs, as measured by the Simpson-Angus Rating Scale. The C-SSRS was administered at baseline and at clinic visits during the treatment and non-treatment follow-up phases. Over half of the patients had a lifetime history of suicidal behavior and/or ideation (62% on varenicline vs. 51% on placebo), but at baseline, no patients in the varenicline group reported suicidal behavior and/or ideation vs. one patient in the placebo group (2%). Suicidal behavior and/or ideation were reported in 11% of the varenicline-treated and 9% of the placebo-treated patients during the treatment phase. During the post-treatment phase, suicidal behavior and/or ideation were reported in 11% of patients in the varenicline group and 5% of patients in the placebo group. Many of the patients reporting suicidal behavior and ideation in the follow-up phase had not reported such experiences in the treatment phase. However, no new suicidal ideation or behavior emerged in either treatment group shortly (within one week) after treatment discontinuation (a phenomenon noted in post-marketing reporting). There were no completed suicides. There was one suicide attempt in a varenicline-treated patient. The limited data available from this single smoking cessation study are not sufficient to allow conclusions to be drawn.

In the trial of patients with MDD, the most common AEs (≥ 10%) in subjects taking varenicline were nausea (27% vs. 10% on placebo), headache (17 vs 11%), abnormal dreams (11% vs 8%), insomnia (11% vs 5%) and irritability (11% vs. 8%). Additionally, the following psychiatric AEs were reported in ≥ 2% of patients in either treatment group (varenicline or placebo, respectively): anxiety (7% vs. 9%), agitation (7% vs. 4%), depressed mood disorders and disturbances (11% vs. 9%), tension (4% vs. 3%), hostility

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(2% vs. 0.4%) and restlessness (2% vs. 2%). Patients treated with varenicline were more likely than patients treated with placebo to report one of various events related to hostility and aggression (3% vs 1%). Psychiatric scales showed no differences between the varenicline and placebo groups and no overall worsening of depression during the study in either treatment group. The percentage of subjects with suicidal ideation and/or behavior was similar between the varenicline and placebo groups during treatment (6% and 8%, respectively) and the non-treatment follow-up (6% and 6%, respectively). There was one event of intentional self-injury/possible suicide attempt during treatment (Day 73) in a subject in the placebo group. Suicide could not be ruled out in one subject who died by an overdose of illicit drugs 76 days after last dose of study drug in the varenicline group.

2.2.4.2 Post-Marketing Experience

The following AEs have been reported during post-approval use of Chantix. Because these events are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

There have been reports of depression, mania, psychosis, hallucinations, paranoia, delusions, homicidal ideation, aggression, hostility, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed suicide in patients attempting to quit smoking while taking Chantix. Smoking cessation with or without treatment is associated with nicotine withdrawal symptoms and the exacerbation of underlying psychiatric illness. Not all patients had known pre-existing psychiatric illness and not all had discontinued smoking.

There have been post-marketing reports of new or worsening seizures in patients treated with Chantix.

There have been post-marketing reports of patients experiencing increased intoxicating effects of alcohol while taking Chantix. Some reported neuropsychiatric events, including unusual and sometimes aggressive behavior.

There have been reports of hypersensitivity reactions, including angioedema.

There have also been reports of serious skin reactions, including Stevens-Johnson Syndrome and erythema multiforme, in patients taking Chantix.

There have been reports of MI and CVA including ischemic and hemorrhagic events in patients taking Chantix. In the majority of the reported cases, patients had pre-existing cardiovascular disease and/or other risk factors. Although smoking is a risk factor for MI and CVA, based on temporal relationship between medication use and events, a contributory role of varenicline cannot be ruled out.

2.2.5 Drug Interactions

Based on varenicline characteristics and clinical experience to date, Chantix has no clinically meaningful pharmacokinetic drug interactions.

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2.2.5.1 Use with Other Drugs for Smoking Cessation

Safety and efficacy of Chantix in combination with other smoking cessation therapies have not been studied.

- Bupropion: Varenicline (1 mg twice daily) did not alter the steady-state pharmacokinetics of bupropion (150 mg twice daily) in 46 smokers. The safety of the combination of bupropion and varenicline has not been established.
- NRT: Although co-administration of varenicline (1 mg twice daily) and transdermal nicotine (21 mg/day) for up to 12 days did not affect nicotine pharmacokinetics, the incidence of nausea, headache, vomiting, dizziness, dyspepsia, and fatigue was greater for the combination than for NRT alone. In this study, eight of twenty-two (36%) patients treated with the combination of varenicline and NRT prematurely discontinued treatment due to AEs, compared to 1 of 17 (6%) of patients treated with NRT and placebo.

2.2.5.2 Effect of Smoking Cessation on Other Drugs

Physiological changes resulting from smoking cessation, with or without treatment with Chantix, may alter the pharmacokinetics or pharmacodynamics of certain drugs (e.g., theophylline, warfarin, insulin) for which dosage adjustment may be necessary.

2.2.6 Use in Specific Populations

2.2.6.1 Pregnancy

The following applies to Category C pregnancy (see FDA Pregnancy Categories), indicating that animal reproduction studies have shown an adverse effect on the fetus and that there are no adequate and well-controlled studies in humans. However, potential benefits may warrant use of the drug in pregnant women despite potential risks.

There are no adequate and well-controlled studies of Chantix use in pregnant women. In animal studies, Chantix caused decreased fetal weights, increased auditory startle response, and decreased fertility in offspring. Chantix should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In reproductive and developmental toxicity studies, pregnant rats and rabbits received varenicline succinate during organogenesis at oral doses up to 15 and 30 mg/kg/day, respectively. These exposures were 36 (rats) and 50 (rabbits) times the human exposure (based on the pharmacokinetic parameter AUC) at the maximum recommended human dose (MRHD) of 1 mg twice daily. While no fetal structural abnormalities occurred in either species, reduced fetal weights occurred in rabbits at the highest dose (exposures 50 times the human exposure at the MRHD based on AUC). Fetal weight reduction did not occur at animal exposures 23 times the human exposure at the MRHD based on AUC.

In a pre-and post-natal development study, pregnant rats received up to 15 mg/kg/day of oral varenicline succinate from organogenesis through lactation. These resulted in exposures up to 36 times the human exposure (based on AUC) at the MRHD of 1 mg twice daily. Decreased fertility and increased auditory startle response occurred in offspring.

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2.2.6.2 Nursing Mothers

It is not known whether Chantix is excreted in human milk. In animal studies varenicline was excreted in milk of lactating animals. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Chantix, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

2.2.6.3 Pediatric Use

Safety and effectiveness of Chantix in pediatric patients have not been established.

2.2.6.4 Geriatric Use

A combined single-and multiple-dose pharmacokinetic study demonstrated that the pharmacokinetics of 1 mg varenicline given once daily or twice daily to 16 healthy elderly male and female smokers (aged 65-75 years) for 7 consecutive days was similar to that of younger subjects. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Varenicline is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

No dosage adjustment is recommended for elderly patients.

2.2.6.5 Renal Impairment

Varenicline is substantially eliminated by renal glomerular filtration along with active tubular secretion. Dose reduction is not required in patients with mild to moderate renal impairment. For patients with severe renal impairment (estimated creatinine clearance < 30 mL/min), and for patients with end-stage renal disease undergoing hemodialysis, dosage adjustment is needed.

2.2.7 Drug Abuse and Dependence

2.2.7.1 Controlled substance

Varenicline is not a controlled substance.

2.2.7.2 Dependence

Humans: Fewer than 1 out of 1000 patients reported euphoria in clinical trials with Chantix. At higher doses (greater than 2 mg), Chantix produced more frequent reports of gastrointestinal disturbances such as nausea and vomiting. There is no evidence of dose-escalation to maintain therapeutic effects in clinical studies, which suggests that tolerance does not develop. Abrupt discontinuation of Chantix was associated with an increase in irritability and sleep disturbances in up to 3% of patients. This suggests that, in some patients, varenicline may produce mild physical dependence which is not associated with addiction.

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In a human laboratory abuse liability study, a single oral dose of 1 mg varenicline did not produce any significant positive or negative subjective responses in smokers. In non-smokers, 1 mg varenicline produced an increase in some positive subjective effects, but this was accompanied by an increase in negative adverse effects, especially nausea. A single oral dose of 3 mg varenicline uniformly produced unpleasant subjective responses in both smokers and non-smokers.

Animals: Studies in rodents have shown that varenicline produces behavioral responses similar to those produced by nicotine. In rats trained to discriminate nicotine from saline, varenicline produced full generalization to the nicotine cue. In self-administration studies, the degree to which varenicline substitutes for nicotine is dependent upon the requirement of the task. Rats trained to self-administer nicotine under easy conditions continued to self-administer varenicline to a degree comparable to that of nicotine; however in a more demanding task, rats self-administered varenicline to a lesser extent than nicotine. Varenicline pre-treatment also reduced nicotine self-administration.

2.2.8 Overdosage

In case of overdose, standard supportive measures should be instituted as required.

Varenicline has been shown to be dialyzed in patients with end stage renal disease, however, there is no experience in dialysis following overdose.

2.3 Bupropion (Zyban)

Bupropion has been developed as a non-tricyclic antidepressant, and is sometimes preferred by smokers who do not wish to use a nicotine-based treatment, or who have already failed to quit using NRT (Cahill 2013). Zyban (bupropion hydrochloride sustained release) has been licensed as a prescription medicine for smoking cessation by the FDA in 1997. In preclinical studies, bupropion reduced nicotine's rewarding effects and attenuated nicotine withdrawal symptoms. Its mechanism of action is thought to be mediated by its ability to block the reuptake of norepinephrine and dopamine in the mesolimbic system and nucleus accumbens, a key area for nicotine reinforcement. Additionally, bupropion antagonizes brain nicotinic receptors and blocks the reinforcing effects of nicotine (Herman 2010).

Unless indicated otherwise, all of the information below has been derived from the FDA-approved Full Prescribing Information for ZYBAN (bupropion hydrochloride) Sustained-Release Tablets, for oral use.

2.3.1 Indications and Usage

Zyban is an aminoketone agent indicated as an aid to smoking cessation treatment. The usual dose of bupropion for smoking cessation is 150 mg once a day for three days increasing to 150 mg twice a day, continued for 7 to 12 weeks. The quit attempt is generally initiated a week after starting pharmacotherapy (Cahill 2013).

2.3.2 Contraindications

- Zyban is contraindicated in patients with a seizure disorder.

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- Zyban is contraindicated in patients with a current or prior diagnosis of bulimia or anorexia nervosa as a higher incidence of seizures was observed in such patients treated with the immediate-release formulation of bupropion.
- Zyban is contraindicated in patients undergoing abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiepileptic drugs.
- The use of monoamine oxidase inhibitors (MAOIs) (intended to treat psychiatric disorders) concomitantly with Zyban or within 14 days of discontinuing treatment with Zyban is contraindicated. There is an increased risk of hypertensive reactions when Zyban is used concomitantly with MAOIs. The use of Zyban within 14 days of discontinuing treatment with an MAOI is also contraindicated. Starting Zyban in a patient treated with reversible MAOIs such as linezolid or intravenous methylene blue is contraindicated.
- Zyban is contraindicated in patients with a known hypersensitivity to bupropion or other ingredients of Zyban. Anaphylactoid/anaphylactic reactions and Stevens-Johnson syndrome have been reported.

2.3.3 Warnings and Precautions

2.3.3.1 Neuropsychiatric Symptoms and Suicide Risk in Smoking Cessation Treatment

Serious neuropsychiatric symptoms have been reported in patients taking Zyban for smoking cessation. These included changes in mood (including depression and mania), psychosis, hallucinations, paranoia, delusions, homicidal ideation, hostility, agitation, aggression, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed suicide. Patients should be observed for the occurrence of neuropsychiatric reactions. In addition, patients should be instructed to contact a healthcare professional if such reactions occur.

In many of these cases, a causal relationship to bupropion treatment is not certain, because depressed mood can be a symptom of nicotine withdrawal. However, some of the cases occurred in patients taking Zyban who continued to smoke.

The risks of Zyban should be weighed against the benefits of its use. Zyban has been demonstrated to increase the likelihood of abstinence from smoking for as long as 6 months compared with treatment with placebo. The health benefits of quitting smoking are immediate and substantial.

2.3.3.2 Suicidal Thoughts and Behaviors in Children, Adolescents, and Young Adults

Patients with MDD, both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern that

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antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment.

Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (selective serotonin re-uptake inhibitors and others) show that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18 to 24) with MDD and other psychiatric disorders. Short-term clinical trials did not show an increase in the risk of suicidality with antidepressants compared with placebo in adults beyond age 24; there was a reduction with antidepressants compared with placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder, or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4,400 subjects. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 subjects. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger subjects for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 subjects treated) are provided in Table 8.

Table 8 Risk Differences in the Number of Suicidality Cases by Age Group in the Pooled Placebo-Controlled Trials of Antidepressants in Pediatric and Adult Subjects

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Subjects Treated
Increases Compared with Placebo	
< 18	14 additional cases
18-24	5 additional cases
Decreases Compared with Placebo	
25-64	1 fewer case
≥ 65	6 fewer cases

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

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All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for MDD as well as for other indications, both psychiatric and non-psychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Families and caregivers of patients being treated with antidepressants for MDD or other indications, both psychiatric and non-psychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to healthcare providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for Zyban should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

2.3.3.3 Seizure

Zyban can cause seizure. The risk of seizure is dose-related. The dose of Zyban should not exceed 300 mg per day. Zyban should be discontinued and treatment should not be restarted if the patient experiences a seizure.

The risk of seizures is also related to patient factors, clinical situations, and concomitant medications that lower the seizure threshold. These risks should be considered before initiating treatment with Zyban. Zyban is contraindicated in patients with a seizure disorder, current or prior diagnosis of anorexia nervosa or bulimia, or undergoing abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiepileptic drugs. The following conditions can also increase the risk of seizure: severe head injury; arteriovenous malformation; central nervous system (CNS) tumor or CNS infection; severe stroke; concomitant use of other medications that lower the seizure threshold (e.g., other bupropion products, antipsychotics, tricyclic antidepressants, theophylline, and systemic corticosteroids), metabolic disorders (e.g., hypoglycemia, hyponatremia, severe hepatic impairment, and hypoxia), use of illicit drugs (e.g., cocaine), or abuse or misuse of prescription drugs such as CNS stimulants. Additional predisposing conditions include diabetes mellitus treated with oral hypoglycemic drugs or insulin; use of anorectic drugs; and excessive use of alcohol, benzodiazepines, sedative/hypnotics, or opiates.

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Incidence of Seizure with Bupropion Use: Doses for smoking cessation should not exceed 300 mg per day. The seizure rate associated with doses of sustained-release bupropion in depressed patients up to 300 mg per day is approximately 0.1% (1/1000) and increases to approximately 0.4% (4/1000) at doses up to 400 mg per day. The risk of seizure can be reduced if the dose of Zyban for smoking cessation does not exceed 300 mg per day, given as 150 mg twice daily, and titration rate is gradual.

2.3.3.4 Interaction with Alcohol

In post-marketing experience, there have been rare reports of adverse neuropsychiatric events or reduced alcohol tolerance in patients who were drinking alcohol during treatment with Zyban. The consumption of alcohol during treatment with Zyban should be minimized or avoided.

2.3.3.5 Hypertension

Treatment with Zyban can result in elevated blood pressure and hypertension. Blood pressure should be assessed before initiating treatment with Zyban, and monitored periodically during treatment. The risk of hypertension is increased if Zyban is used concomitantly with MAOIs or other drugs that increase dopaminergic or noradrenergic activity.

Data from a comparative trial of Zyban, NTS, the combination of Zyban plus NTS, and placebo as an aid to smoking cessation suggest a higher incidence of treatment emergent hypertension in patients treated with the combination of Zyban and NTS. In this trial, 6.1% of subjects treated with the combination of Zyban and NTS had treatment-emergent hypertension compared to 2.5%, 1.6%, and 3.1% of subjects treated with Zyban, NTS, and placebo, respectively. The majority of these subjects had evidence of pre-existing hypertension. Three subjects (1.2%) treated with the combination of Zyban and NTS and 1 subject (0.4%) treated with NTS had study medication discontinued due to hypertension compared with none of the subjects treated with Zyban or placebo. Monitoring of blood pressure is recommended in patients who receive the combination of bupropion and nicotine replacement.

In a clinical trial of bupropion immediate-release in MDD subjects with stable congestive heart failure (N=36), bupropion was associated with an exacerbation of pre-existing hypertension in 2 subjects, leading to discontinuation of bupropion treatment. There are no controlled trials assessing the safety of bupropion in patients with a recent history of MI or unstable cardiac disease.

2.3.3.6 Activation of Mania/Hypomania

Antidepressant treatment can precipitate a manic, mixed, or hypomanic episode. The risk appears to be increased in patients with bipolar disorder or who have risk factors for bipolar disorder. There were no reports of activation of psychosis or mania in clinical trials with Zyban conducted in non-depressed smokers. Bupropion is not approved for use in treating bipolar depression.

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2.3.3.7 Psychosis and Other Neuropsychiatric Reactions

Depressed patients treated with bupropion in depression trials have had a variety of neuropsychiatric signs and symptoms, including delusions, hallucinations, psychosis, concentration disturbance, paranoia, and confusion. Some of these patients had a diagnosis of bipolar disorder. In some cases, these symptoms abated upon dose reduction and/or withdrawal of treatment. Patients should be instructed to contact a healthcare professional if such reactions occur.

In clinical trials with Zyban conducted in non-depressed smokers, the incidence of neuropsychiatric side effects was generally comparable to placebo. However, in the post-marketing experience, patients taking Zyban to quit smoking have reported similar types of neuropsychiatric symptoms to those reported by patients in the clinical trials of bupropion for depression.

2.3.3.8 Angle-Closure Glaucoma

The pupillary dilation that occurs following use of many antidepressant drugs including bupropion may trigger an angle-closure attack in a patient with anatomically narrow angles who does not have a patent iridectomy.

2.3.3.9 Hypersensitivity Reactions

Anaphylactoid/anaphylactic reactions have occurred during clinical trials with bupropion. Reactions have been characterized by pruritus, urticaria, angioedema, and dyspnea requiring medical treatment. In addition, there have been rare, spontaneous post-marketing reports of erythema multiforme, Stevens-Johnson syndrome, and anaphylactic shock associated with bupropion. Instruct patients to discontinue Zyban and consult a healthcare provider if they develop an allergic or anaphylactoid/anaphylactic reaction (e.g., skin rash, pruritus, hives, chest pain, edema, and shortness of breath) during treatment.

There are reports of arthralgia, myalgia, fever with rash and other serum sickness-like symptoms suggestive of delayed hypersensitivity.

2.3.4 Adverse Reactions

The following adverse reactions are discussed in greater detail in Section 2.3.3:

- Neuropsychiatric symptoms and suicide risk in smoking cessation treatment
- Suicidal thoughts and behaviors in adolescents and young adults
- Seizure
- Hypertension
- Activation of mania or hypomania
- Psychosis and other neuropsychiatric reactions
- Angle-closure glaucoma
- Hypersensitivity reactions

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2.3.4.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Adverse Reactions Leading to Discontinuation of Treatment: Adverse reactions were sufficiently troublesome to cause discontinuation of treatment in 8% of the 706 subjects treated with Zyban and 5% of the 313 patients treated with placebo. The more common events leading to discontinuation of treatment with Zyban included nervous system disturbances (3.4%), primarily tremors, and skin disorders (2.4%), primarily rashes.

Commonly Observed Adverse Reactions: The most commonly observed adverse reactions consistently associated with the use of Zyban were dry mouth and insomnia. The incidence of dry mouth and insomnia may be related to the dose of Zyban. The occurrence of these adverse reactions may be minimized by reducing the dose of Zyban. In addition, insomnia may be minimized by avoiding bedtime doses.

Adverse reactions reported in the dose-response and comparator trials are presented in Table 9 and Table 10, respectively. Reported adverse reactions were classified using a Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART)-based dictionary.

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Table 9 Adverse Reactions Reported by at Least 1% of Subjects and at a Greater Frequency than Placebo in the Dose-Response Trial

Adverse Reaction (%)	Zyban 100 to 300 mg/day (N=461)	Placebo (N=150)
Body (General)		
Neck pain	2	< 1
Allergic reaction	1	0
Cardiovascular		
Hot flashes	1	0
Hypertension	1	< 1
Digestive		
Dry mouth	11	5
Increased appetite	2	< 1
Anorexia	1	< 1
Musculoskeletal		
Arthralgia	4	3
Myalgia	2	1
Nervous system		
Insomnia	31	21
Dizziness	8	7
Tremor	2	1
Somnolence	2	1
Thinking abnormality	1	0
Respiratory		
Bronchitis	2	0
Skin		
Pruritus	3	< 1
Rash	3	< 1
Dry skin	2	0
Urticaria	1	0
Special senses		
Taste perversion	2	< 1

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Table 10 Adverse Reactions Reported by at Least 1% of Subjects on Active Treatment and at a Greater Frequency than Placebo in the Comparator Trial

Adverse Experience (%) (COSTART Term)	Zyban 300 mg/day (N=243)	NTS 21 mg/day (N=243)	Zyban and NTS (N=244)	Placebo (N=159)
Body				
Abdominal pain	3	4	1	1
Accidental injury	2	2	1	1
Chest pain	< 1	1	3	1
Neck pain	2	1	< 1	0
Facial edema	< 1	0	1	0
Cardiovascular				
Hypertension	1	< 1	2	0
Palpitations	2	0	1	0
Digestive				
Nausea	9	7	11	4
Dry mouth	10	4	9	4
Constipation	8	4	9	3
Diarrhea	4	4	3	1
Anorexia	3	1	5	1
Mouth ulcer	2	1	1	1
Thirst	< 1	< 1	2	0
Musculoskeletal				
Myalgia	4	3	5	3
Arthralgia	5	3	3	2
Nervous system				
Insomnia	40	28	45	18
Dream abnormality	5	18	13	3
Anxiety	8	6	9	6
Disturbed concentration	9	3	9	4
Dizziness	10	2	8	6
Nervousness	4	< 1	2	2
Tremor	1	< 1	2	0
Dysphoria	< 1	1	2	1

table continues

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Adverse Experience (%) (COSTART Term)	Zyban 300 mg/day (N=243)	NTS 21 mg/day (N=243)	Zyban and NTS (N=244)	Placebo (N=159)
Respiratory				
Rhinits	12	11	9	8
Increased cough	3	5	< 1	1
Pharyngitis	3	2	3	0
Sinusitis	2	2	2	1
Dyspnea	1	0	2	1
Epistaxis	2	1	1	0
Skin				
Application site reaction [a]	11	17	15	7
Rash	4	3	3	2
Pruritus	3	1	5	1
Urticaria	2	0	2	0
Special senses				
Taste perversion	3	1	3	2
Tinnitus	1	0	< 1	0

[a] Subjects randomized to Zyban or placebo received placebo patches

Adverse reactions in a 1-year maintenance trial and a 12-week COPD trial with Zyban were quantitatively and qualitatively similar to those observed in the dose-response and comparator trials.

Other Adverse Reactions Observed during the Clinical Development of Bupropion: In addition to the adverse reactions noted above, the following adverse reactions have been reported in clinical trials with the sustained-release formulation of bupropion in depressed subjects and in non-depressed smokers, as well as in clinical trials with the immediate-release formulation of bupropion.

Adverse reaction frequencies represent the proportion of subjects who experienced a treatment-emergent adverse reaction on at least one occasion in placebo-controlled trials for depression (n = 987) or smoking cessation (n = 1013), or subjects who experienced an adverse reaction requiring discontinuation of treatment in an open-label surveillance trial with bupropion sustained-release tablets (n = 3100). All treatment-emergent adverse reactions are included except those listed in Table 9 and Table 10, those listed in other safety-related sections, those subsumed under COSTART terms that are either overly general or excessively specific so as to be uninformative, those not reasonably associated

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with the use of the drug, and those that were not serious and occurred in fewer than 2 subjects.

Adverse reactions are further categorized by body system and listed in order of decreasing frequency according to the following definitions of frequency: Frequent adverse reactions are defined as those occurring in at least 1/100 subjects. Infrequent adverse reactions are those occurring in 1/100 to 1/1000 subjects, while rare events are those occurring in less than 1/1000 subjects.

- Body (General): *Frequent:* asthenia, fever, and headache. *Infrequent:* chills, inguinal hernia, and photosensitivity. *Rare:* malaise.
- Cardiovascular: *Infrequent:* flushing, migraine, postural hypotension, stroke, tachycardia, and vasodilation. *Rare:* syncope.
- Digestive: *Frequent:* dyspepsia and vomiting. *Infrequent:* abnormal liver function, bruxism, dysphagia, gastric reflux, gingivitis, jaundice, and stomatitis.
- Hemic and Lymphatic: *Infrequent:* ecchymosis.
- Metabolic and Nutritional: *Infrequent:* edema and peripheral edema.
- Musculoskeletal: *Infrequent:* leg cramps and twitching.
- Nervous System: *Frequent:* agitation, depression, and irritability. *Infrequent:* abnormal coordination, CNS stimulation, confusion, decreased libido, decreased memory, depersonalization, emotional lability, hostility, hyperkinesia, hypertonia, hypesthesia, paresthesia, suicidal ideation, and vertigo. *Rare:* amnesia, ataxia, derealization, and hypomania.
- Respiratory: *Rare:* bronchospasm.
- Skin: *Frequent:* sweating.
- Special Senses: *Frequent:* blurred vision or diplopia. *Infrequent:* accommodation abnormality and dry eye.
- Urogenital: *Frequent:* urinary frequency. *Infrequent:* impotence, polyuria, and urinary urgency.

2.3.4.2 Post-marketing experience

The following adverse reactions have been identified during post-approval use of Zyban and are not described elsewhere in the report. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a relationship to drug exposure.

- Body (General): Arthralgia, myalgia, and fever with rash and other symptoms suggestive of delayed hypersensitivity. These symptoms may resemble serum sickness.
- Cardiovascular: Cardiovascular disorder, complete atrioventricular block, extrasystoles, hypotension, MI, phlebitis, and pulmonary embolism.

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- Digestive: Colitis, esophagitis, gastrointestinal hemorrhage, gum hemorrhage, hepatitis, increased salivation, intestinal perforation, liver damage, pancreatitis, stomach ulcer, and stool abnormality.
- Endocrine: Hyperglycemia, hypoglycemia, and syndrome of inappropriate antidiuretic hormone.
- Hemic and Lymphatic: Anemia, leukocytosis, leukopenia, lymphadenopathy, pancytopenia, and thrombocytopenia. Altered prothrombin time and/or international normalized ratio, infrequently associated with hemorrhagic or thrombotic complications, were observed when bupropion was co-administered with warfarin.
- Metabolic and Nutritional: Glycosuria.
- Musculoskeletal: Arthritis and muscle rigidity/fever/rhabdomyolysis, and muscle weakness.
- Nervous System: Abnormal electroencephalogram, aggression, akinesia, aphasia, coma, completed suicide, delirium, delusions, dysarthria, dyskinesia, dystonia, euphoria, extrapyramidal syndrome, hallucinations, hypokinesia, increased libido, manic reaction, neuralgia, neuropathy, paranoid ideation, restlessness, suicide attempt, and unmasking tardive dyskinesia.
- Respiratory: Pneumonia.
- Skin: Alopecia, angioedema, exfoliative dermatitis, hirsutism, and Stevens-Johnson syndrome.
- Special Senses: Deafness, increased intraocular pressure, and mydriasis.
- Urogenital: Abnormal ejaculation, cystitis, dyspareunia, dysuria, gynecomastia, menopause, painful erection, prostate disorder, salpingitis, urinary incontinence, urinary retention, urinary tract disorder, and vaginitis.

2.3.5 Drug Interactions

2.3.5.1 Potential for Other Drugs to Affect Zyban

Bupropion is primarily metabolized to hydroxybupropion by CYP2B6. Therefore, the potential exists for drug interactions between Zyban and drugs that are inhibitors or inducers of CYP2B6.

Inhibitors of CYP2B6: *Ticlopidine and Clopidogrel:* Concomitant treatment with these drugs can increase bupropion exposure but decrease hydroxybupropion exposure. Based on clinical response, dosage adjustment of Zyban may be necessary when co-administered with CYP2B6 inhibitors (e.g., ticlopidine or clopidogrel).

Inducers of CYP2B6: *Ritonavir, Lopinavir, and Efavirenz:* Concomitant treatment with these drugs can decrease bupropion and increase hydroxybupropion exposure. Dosage increase of Zyban may be necessary when co-administered with ritonavir, lopinavir, or efavirenz but should not exceed the maximum recommended dose.

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Carbamazepine, Phenobarbital, Phenytoin: While not systematically studied, these drugs may induce the metabolism of bupropion and may decrease bupropion exposure. If bupropion is used concomitantly with a CYP inducer, it may be necessary to increase the dose of bupropion, but the maximum recommended dose should not be exceeded.

2.3.5.2 Potential for Zyban to Affect Other Drugs

Drugs Metabolized by CYP2D6: Bupropion and its metabolites (erythrohydrobupropion, threohydrobupropion, hydroxybupropion) are CYP2D6 inhibitors. Therefore, co-administration of Zyban with drugs that are metabolized by CYP2D6 can increase the exposures of drugs that are substrates of CYP2D6. Such drugs include certain antidepressants (e.g., venlafaxine, nortriptyline, imipramine, desipramine, paroxetine, fluoxetine, and sertraline), antipsychotics (e.g., haloperidol, risperidone, thioridazine), beta-blockers (e.g., metoprolol), and Type 1C antiarrhythmics (e.g., propafenone and flecainide). When used concomitantly with Zyban, it may be necessary to decrease the dose of these CYP2D6 substrates, particularly for drugs with a narrow therapeutic index.

Drugs that require metabolic activation by CYP2D6 to be effective (e.g., tamoxifen) theoretically could have reduced efficacy when administered concomitantly with inhibitors of CYP2D6 such as bupropion. Patients treated concomitantly with Zyban and such drugs may require increased doses of the drug.

2.3.5.3 Drugs that Lower Seizure Threshold

Extreme caution should be used when co-administering Zyban with other drugs that lower seizure threshold (e.g., other bupropion products, antipsychotics, antidepressants, theophylline, or systemic corticosteroids). Low initial doses should be used and the dose should be increased gradually.

2.3.5.4 Dopaminergic Drugs (Levodopa and Amantadine)

Bupropion, levodopa, and amantadine have dopamine agonist effects. CNS toxicity has been reported when bupropion was co-administered with levodopa or amantadine. Adverse reactions have included restlessness, agitation, tremor, ataxia, gait disturbance, vertigo, and dizziness. It is presumed that the toxicity results from cumulative dopamine agonist effects. Caution should be used when administering Zyban concomitantly with these drugs.

2.3.5.5 MAO Inhibitors

Bupropion inhibits the reuptake of dopamine and norepinephrine. Concomitant use of MAOIs and bupropion is contraindicated because there is an increased risk of hypertensive reactions if bupropion is used concomitantly with MAOIs. Studies in animals demonstrate that the acute toxicity of bupropion is enhanced by the MAO inhibitor phenelzine. At least 14 days should elapse between discontinuation of an MAOI and initiation of treatment with Zyban. Conversely, at least 14 days should be allowed after stopping Zyban before starting an MAOI intended to treat psychiatric disorders.

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2.3.5.6 Smoking Cessation

Physiological changes resulting from smoking cessation, with or without treatment with Zyban, may alter the pharmacokinetics or pharmacodynamics of certain drugs (e.g., theophylline, warfarin, insulin) for which dosage adjustment may be necessary.

2.3.5.7 Drug-Laboratory Test Interactions

False-positive urine immunoassay screening tests for amphetamines have been reported in patients taking bupropion. This is due to lack of specificity of some screening tests. False-positive test results may result even following discontinuation of bupropion therapy. Confirmatory tests, such as gas chromatography/mass spectrometry, will distinguish bupropion from amphetamines.

2.3.6 Use in Specific Populations

2.3.6.1 Pregnancy

The following applies to Category C pregnancy (see 2.2.6.1 and FDA Pregnancy Categories).

Risk Summary: Data from epidemiological studies of pregnant women exposed to bupropion in the first trimester indicate no increased risk of congenital malformations overall. All pregnancies, regardless of drug exposure, have a background rate of 2% to 4% for major malformations, and 15% to 20% for pregnancy loss. No clear evidence of teratogenic activity was found in reproductive developmental studies conducted in rats and rabbits; however, in rabbits, slightly increased incidences of fetal malformations and skeletal variations were observed at doses approximately 2 times the MRHD and greater, and decreased fetal weights were seen at doses three times the MRHD and greater. Zyban should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical Considerations: Pregnant smokers should be encouraged to attempt cessation using educational and behavioral interventions before pharmacological approaches are used.

Human Data: Data from the international bupropion Pregnancy Registry (675 first trimester exposures) and a retrospective cohort study using the United Healthcare database (1,213 first trimester exposures) did not show an increased risk for malformations overall.

No increased risk for cardiovascular malformations overall has been observed after bupropion exposure during the first trimester. The prospectively observed rate of cardiovascular malformations in pregnancies with exposure to bupropion in the first trimester from the international Pregnancy Registry was 1.3% (9 cardiovascular malformations/675 first trimester maternal bupropion exposures), which is similar to the background rate of cardiovascular malformations (approximately 1%). Data from the United Healthcare database and a case-control study (6,853 infants with cardiovascular malformations and 5,763 with non-cardiovascular malformations) from the National Birth Defects Prevention Study (NBDPS) did not show an increased risk for cardiovascular malformations overall after bupropion exposure during the first trimester.

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Study findings on bupropion exposure during the first trimester and risk for left ventricular outflow tract obstruction (LVOTO) are inconsistent and do not allow conclusions regarding a possible association. The United Healthcare database lacked sufficient power to evaluate this association; the NBDPS found increased risk for LVOTO (n = 10; adjusted odds ratio [OR] = 2.6; 95% CI: 1.2, 5.7), and the Slone Epidemiology case control study did not find increased risk for LVOTO.

Study findings on bupropion exposure during the first trimester and risk for ventricular septal defect (VSD) are inconsistent and do not allow conclusions regarding a possible association. The Slone Epidemiology Study found an increased risk for VSD following first trimester maternal bupropion exposure (n = 17; adjusted OR = 2.5; 95% CI: 1.3, 5.0) but did not find increased risk for any other cardiovascular malformations studied (including LVOTO as above). The NBDPS and United Healthcare database study did not find an association between first trimester maternal bupropion exposure and VSD.

For the findings of LVOTO and VSD, the studies were limited by the small number of exposed cases, inconsistent findings among studies, and the potential for chance findings from multiple comparisons in case control studies.

Animal Data: In studies conducted in rats and rabbits, bupropion was administered orally during the period of organogenesis at doses of up to 450 and 150 mg per kg per day, respectively (approximately 15 and 10 times the MRHD respectively, on a mg per m^2 basis). No clear evidence of teratogenic activity was found in either species; however, in rabbits, slightly increased incidences of fetal malformations and skeletal variations were observed at the lowest dose tested (25 mg per kg per day, approximately 2 times the MRHD on a mg per m^2 basis) and greater. Decreased fetal weights were observed at 50 mg per kg and greater.

When rats were administered bupropion at oral doses of up to 300 mg per kg per day (approximately 10 times the MRHD on a mg per m^2 basis) prior to mating and throughout pregnancy and lactation, there were no apparent adverse effects on offspring development.

2.3.6.2 Nursing Mothers

Bupropion and its metabolites are present in human milk. In a lactation study of 10 women, levels of orally dosed bupropion and its active metabolites were measured in expressed milk. The average daily infant exposure (assuming 150 mL per kg daily consumption) to bupropion and its active metabolites was 2% of the maternal weight-adjusted dose. Caution should be exercised when Zyban is administered to a nursing woman.

2.3.6.3 Pediatric Use

Safety and effectiveness in the pediatric population have not been established.

2.3.6.4 Geriatric Use

Of the approximately 6000 subjects who participated in clinical trials with bupropion sustained-release tablets (depression and smoking cessation trials), 275 were aged ≥ 65 years and 47 were aged ≥ 75 years. In addition, several hundred subjects aged ≥ 65 years

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participated in clinical trials using the immediate-release formulation of bupropion (depression trials). No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Bupropion is extensively metabolized in the liver to active metabolites, which are further metabolized and excreted by the kidneys. The risk of adverse reactions may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, it may be necessary to consider this factor in dose selection; it may be useful to monitor renal function.

2.3.6.5 Renal Impairment

A reduced dose and/or dosing frequency of Zyban should be considered in patients with renal impairment (Glomerular Filtration Rate: less than 90 mL per min). Bupropion and its metabolites are cleared renally and may accumulate in such patients to a greater extent than usual. Adverse reactions that could indicate high bupropion or metabolite exposures should be closely monitored for.

2.3.6.6 Hepatic Impairment

In patients with moderate to severe hepatic impairment (Child-Pugh score: 7 to 15), the maximum dose of Zyban is 150 mg every other day. In patients with mild hepatic impairment (Child-Pugh score: 5 to 6), reducing the dose and/or frequency of dosing should be considered.

2.3.7 Drug Abuse and Dependence

2.3.7.1 Controlled Substance

Bupropion is not a controlled substance.

2.3.7.2 Abuse

Humans: Controlled clinical trials conducted in normal volunteers, in subjects with a history of multiple drug abuse, and in depressed subjects showed some increase in motor activity and agitation/excitement, often typical of central stimulant activity.

In a population of individuals experienced with drugs of abuse, a single oral dose of 400 mg of bupropion produced mild amphetamine-like activity as compared with placebo on the Morphine-Benzedrine Subscale of the Addiction Research Center Inventories (ARCI) and a score greater than placebo but less than 15 mg of the Schedule II stimulant dextroamphetamine on the Liking Scale of the ARCI. These scales measure general feelings of euphoria and drug liking which are often associated with abuse potential.

Findings in clinical trials, however, are not known to reliably predict the abuse potential of drugs. Nonetheless, evidence from single-dose trials does suggest that the recommended daily dosage of bupropion when administered orally in divided doses is not likely to be significantly reinforcing to amphetamine or CNS stimulant abusers. However, higher doses (that could not be tested because of the risk of seizure) might be modestly attractive to those who abuse CNS stimulant drugs.

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Zyban is intended for oral use only. The inhalation of crushed tablets or injection of dissolved bupropion has been reported. Seizures and/or cases of death have been reported when bupropion has been administered intranasally or by parenteral injection.

Animals: Studies in rodents and primates demonstrated that bupropion exhibits some pharmacologic actions common to psychostimulants. In rodents, it has been shown to increase locomotor activity, elicit a mild stereotyped behavior response, and increase rates of responding in several schedule-controlled behavior paradigms. In primate models assessing the positive reinforcing effects of psychoactive drugs, bupropion was self-administered intravenously. In rats, bupropion produced amphetamine-like and cocaine-like discriminative stimulus effects in drug discrimination paradigms used to characterize the subjective effects of psychoactive drugs.

The possibility that bupropion may induce dependence should be kept in mind when evaluating the desirability of including the drug in smoking cessation programs of individual patients.

2.3.8 Overdosage

2.3.8.1 Human Overdose Experience

Overdoses of up to 30 grams or more of bupropion have been reported. Seizure was reported in approximately one-third of all cases. Other serious reactions reported with overdoses of bupropion alone included hallucinations, loss of consciousness, sinus tachycardia, and electrocardiogram changes such as conduction disturbances (including QRS prolongation) or arrhythmias. Fever, muscle rigidity, rhabdomyolysis, hypotension, stupor, coma, and respiratory failure have been reported mainly when bupropion was part of multiple drug overdoses.

Although most patients recovered without sequelae, deaths associated with overdoses of bupropion alone have been reported in patients ingesting large doses of the drug. Multiple uncontrolled seizures, bradycardia, cardiac failure, and cardiac arrest prior to death were reported in these patients.

2.3.8.2 Overdosage Management

In case of overdose a Certified Poison Control Center should be contacted for up–to-date guidance and advice.

There are no known antidotes for bupropion. In case of an overdose, supportive care, including close medical supervision and monitoring, should be provided. The possibility of multiple drug overdose should be considered. An adequate airway, oxygenation, and ventilation should be ensured, and cardiac rhythm and vital signs should be monitored. Induction of emesis is not recommended.

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3 REFERENCES

Scientific Articles

Cahill K, Stevens S, Perera R, Lancaster T. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. Cochrane Database Syst Rev. 2013;5(5).

Herman AI, Sofuoglu M. Comparison of available treatments for tobacco addiction. Curr Psychiatry Rep. 2010;12(5): 433–440.

Stead LF, Perera R, Bullen C, Mant D, Hartmann-Boyce J, Cahill K, et al. Nicotine replacement therapy for smoking cessation. Cochrane Database Syst Rev. 2012;11(11).

Electronic Material

Drugs@FDA: FDA Approved Drug Products [Internet]. US Food and Drug Administration. Available from: www.accessdata.fda.gov/scripts/cder/drugsatfda/.

FDA 101: Smoking Cessation Products [Internet]. US Food and Drug Administration. Available from: http://www.fda.gov/downloads/forconsumers/consumerupdates/ucm331925.pdf.

FDA Pregnancy Categories [Internet]. US Food and Drug Administration. Available from: http://www.drugs.com/pregnancy-categories.html.

Prescribing Information and Label

GlaxoSmithKline Consumer Healthcare, LP. NicoDerm CQ, Nicotine Transdermal System: Drug Facts. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020165Orig1s036lbl.pdf (label approved on 07/Oct/2015)

GlaxoSmithKline Consumer Healthcare, LP. Nicorette, Nicotine Polacrilex Gum: Drug Facts. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/018612s076lbl.pdf (label approved on 30/Sep/2015).

GlaxoSmithKline Consumer Healthcare, LP. Nicorette, Nicotine Polacrilex Lozenge: Drug Facts. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/022360s010lbl.pdf (label approved on 30/Sep/2015).

GlaxoSmithKline. ZYBAN (bupropion hydrochloride) Sustained-Release Tablets, for oral use: Full Prescribing Information. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/020711s042lbl.pdf (label approved on 24/Dec/2014).

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Novartis Consumer Health, Inc. Habitrol Take Control, Nicotine Transdermal System Patch: Drug Facts. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/020076Orig1s036lbl.pdf (label approved on 25/Jul/2014).

Pfizer Labs. CHANTIX (varenicline) Tablets: Full Prescribing Information. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021928s033s034s037lbl.pdf (label approved on 15/Oct/2014).

Pharmacia & Upjohn Co, Division of Pfizer Inc. Nicotrol inhaler (nicotine inhalation system). Available from: http://www.pfizer.com/files/products/uspi_nicotrol_inhaler.pdf (label revised Dec 2008).

Pharmacia & Upjohn Co, Division of Pfizer Inc. Nicotrol NS (nicotine nasal spray). Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020385s010lbl.pdf (label approved on 29/Jun/2010).

Watson Laboratories. Nicotine Polacrilex Gum USP. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/74-507_Nicotine_prntlbl.pdf (label approved on 15/Mar/1999).

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