PRODUCT MONOGRAPH

PrCHAMPIX®

(varenicline tartrate tablets)

0.5 mg and 1.0 mg varenicline (as varenicline tartrate)

Smoking-Cessation Aid

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Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION....3
SUMMARY PRODUCT INFORMATION....3
INDICATIONS AND CLINICAL USE....3
CONTRAINDICATIONS....3
WARNINGS AND PRECAUTIONS....4
ADVERSE REACTIONS....12
DRUG INTERACTIONS....23
DOSAGE AND ADMINISTRATION....26
OVERDOSAGE....29
ACTION AND CLINICAL PHARMACOLOGY....29
STORAGE AND STABILITY....34
DOSAGE FORMS, COMPOSITION AND PACKAGING....35

PART II: SCIENTIFIC INFORMATION....36
PHARMACEUTICAL INFORMATION....36
CLINICAL TRIALS....37
DETAILED PHARMACOLOGY....42
TOXICOLOGY....43
REFERENCES....46

PART III: CONSUMER INFORMATION....49

CHAMPIX®
(varenicline tartrate tablets)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Non-medicinal Ingredients
oral	Tablet: 0.5 mg and 1.0 mg	Anhydrous dibasic calcium phosphate, colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, and microcrystalline cellulose. The film-coating contains hypromellose, polyethylene glycol, titanium dioxide and triacetin. The 1.0 mg tablet also contains FD&C Blue #2/Indigo Carmine Aluminum Lake as a colouring agent.

INDICATIONS AND CLINICAL USE

Adults
CHAMPIX (varenicline tartrate) is indicated for smoking-cessation treatment in adults, in conjunction with smoking-cessation counselling.

See **Serious WARNINGS AND PRECAUTIONS, Psychiatric Symptoms**.

Prior to a decision to prescribe non-nicotine treatment including CHAMPIX, thorough consideration should be given to the treatment option of nicotine replacement therapy.

Geriatrics (>65 years of age): No dosage adjustment is necessary for healthy elderly patients. However, 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 (see **WARNINGS AND PRECAUTIONS, Special Populations: Geriatrics**).

Pediatrics (<18 years of age): The safety and efficacy of varenicline in pediatric patients have not been established, therefore its use in this patient population is not recommended (see **WARNINGS AND PRECAUTIONS**, **Special Populations: Pediatrics**).

CONTRAINDICATIONS

Patients who are hypersensitive to varenicline or to any ingredient in the formulation or component of the container.

WARNINGS AND PRECAUTIONS

Serious WARNINGS and PRECAUTIONS

Psychiatric Symptoms:
There have been post-marketing reports of serious neuropsychiatric symptoms in patients being treated with CHAMPIX (varenicline tartrate), including depressed mood, agitation, aggression, hostility, changes in behavior, suicide related events, including ideation, behavior, attempted suicide and suicide, as well as worsening of pre-existing psychiatric disorder. **These events have occurred in patients with and without pre-existing psychiatric disorders** (see also **WARNINGS AND PRECAUTIONS**, **Psychiatric Symptoms**).

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 CHAMPIX who continued to smoke. All patients being treated with CHAMPIX should be observed for neuropsychiatric symptoms.

Important Recommendations Regarding Psychiatric Symptoms:

- The benefits and risks of all options for quitting smoking should be discussed with the patient before initiating treatment.
- All patients attempting to quit smoking with CHAMPIX, as well as their families and caregivers, should be alerted about the need to monitor for depressed mood, agitation, aggression, hostility, suicidal ideation or behavior, or changes in behavior or thinking that are not typical for the patient.
- Patients should be instructed to stop taking CHAMPIX immediately and contact their doctor if they experience, or if others observe, these symptoms. In many post-marketing cases, resolution of symptoms after discontinuation of CHAMPIX was reported, although in some cases the symptoms persisted; therefore, ongoing monitoring and supportive care should be provided until symptoms resolve.
- **Regarding alcohol intake**: Patients should be advised that alcohol intake may increase the risk of experiencing psychiatric adverse events during treatment with CHAMPIX.
- **Regarding patients with psychiatric history:** Patients with concomitant psychiatric conditions, even if well controlled, or with a history of psychiatric symptoms, should be diligently monitored by a healthcare professional for new or worsened psychiatric events.

Psychiatric Symptoms (see also **ADVERSE REACTIONS, Post-Marketing Experience**). There have been post-marketing reports of serious neuropsychiatric symptoms in patients being treated with CHAMPIX, including anxiety, psychosis, mood swings, depressed mood, agitation, aggression, hostility, changes in behavior or thinking, suicidal ideation, suicidal behavior and suicide, as well as worsening of pre-existing psychiatric disorder (previously diagnosed or not) (see **Serious WARNINGS and PRECAUTIONS).**

There are a number of confounding factors which may have contributed, including effects of nicotine withdrawal due to partial or complete smoking discontinuation; concomitant, or history of psychiatric conditions; and the concomitant use of other CNS drugs and/or alcohol. However, there are cases for which these confounding factors did not appear to be present, including cases where symptoms occurred within the first week of initiating CHAMPIX, prior to initiating smoking cessation. There have been other cases where symptoms developed following cessation of CHAMPIX therapy.

It is not known whether these events are occurring at a rate and severity which is different from the background rate for smoking cessation in the general population, or in the psychiatric population (treated or untreated), or different from the rates for other drugs in the class of smoking cessation (see **ADVERSE REACTIONS**, **Neuropsychiatric Adverse Events in Randomized, Double-blind, Placebo-Controlled Clinical Studies of Varenicline**).

Pre-existing Psychiatric Disorder or Symptoms

Patients with concomitant psychiatric conditions, even if well controlled, or with a history of psychiatric symptoms should be diligently monitored by a health care professional for new or worsened psychiatric events (see Psychiatric Symptoms, above, WARNINGS AND PRECAUTIONS). Care should be taken with patients with a history of psychiatric illness and patients should be advised accordingly.

Patients with certain serious psychiatric disorders such as schizophrenia, bipolar disorder and major depressive disorder did not participate in the pre-marketing studies of CHAMPIX**.** Smoking cessation studies subsequent to CHAMPIX marketing provided limited data in patients with stable schizophrenia schizoaffective disorder (n=128) and in patients with major depressive disorder (n=525) (See **Special Populations, Use of CHAMPIX in Patients with Concomitant Conditions, Psychiatric Patients and ACTIONS AND CLINICAL PHARMACOLOGY, Study in Subjects with Stable Schizophrenia or Schizoaffective Disorder, Patients with Major Depressive Disorder).**

Angioedema and Hypersensitivity reactions
There have been post-marketing reports of hypersensitivity reactions, including angioedema, in patients treated with CHAMPIX (see **ADVERSE REACTIONS, Post-Marketing Experience**). Clinical signs included swelling of the face, mouth (tongue, lips and gums), neck (pharynx and larynx) and extremities. There were rare reports of life-threatening angioedema requiring urgent medical attention due to respiratory compromise. Patients experiencing these symptoms should be instructed to discontinue treatment with CHAMPIX and contact a healthcare provider immediately.

Serious Skin Reactions

There have also been post-marketing reports of rare but severe cutaneous reactions, including Stevens-Johnson syndrome and erythema multiforme, in patients using CHAMPIX (see **ADVERSE REACTIONS, Post-Marketing Experience**). As these skin reactions can be life-threatening, patients should be instructed to discontinue treatment at the first sign of rash or skin reaction and contact a healthcare provider immediately.

Seizures

In clinical trials and post-marketing experience there have been reports of seizures in patients treated with CHAMPIX. Some patients had no history of seizures, whereas others had a history of seizure disorder that was remote or well-controlled. CHAMPIX should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold. Advise patients to discontinue CHAMPIX and immediately contact a healthcare provider if they experience a seizure while on treatment (see **Special Populations, Use of CHAMPIX in Patients with Concomitant Conditions).**

Cardiovascular Events

In a placebo-controlled smoking cessation clinical trial in patients with stable cardiovascular disease (CVD), patients were treated with CHAMPIX 1 mg BID or placebo for 12 weeks, and then followed for another 40 weeks. There were approximately 350 patients per arm.

Serious cardiovascular (CV) events that were reported more frequently in CHAMPIX compared to placebo (difference > 2 subjects) were: non-fatal myocardial infarctions (4 vs. 1, on-treatment phase) and need for coronary revascularization (7 vs. 2, post-treatment phase). The total number of patients that experienced serious CV events in CHAMPIX compared to placebo was: 10 vs. 9 on treatment phase, 16 vs. 11 post-treatment phase, for a total of 25 vs. 20 over the 52 week duration. The serious CV events occurring during the treatment and post-treatment phases were adjudicated by an independent blinded committee.

The study was powered for assessing efficacy (ie quit rates) but not for assessing differences in the occurrence of serious CV events between CHAMPIX and placebo. Therefore, the study was not large enough to allow conclusions regarding the difference in the incidence of CV events reported in the two arms (See also **ADVERSE EVENTS, Clinical Trial in Special Populations**; and **ACTION AND CLINICAL PHARMACOLOGY**, Special Population). Physicians are to inform patients of the symptoms of a heart attack and stroke, and instruct them to get emergency medical help right away if they experience any of these symptoms (see also **Patient Counselling Information**).

CHAMPIX has not been studied in patients with unstable cardiovascular disease or those with cardiovascular events occurring within two months before study screening. Patients should be advised to notify a health care provider of new or worsening symptoms of cardiovascular disease. The risks of CHAMPIX 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. CHAMPIX has been demonstrated to increase the likelihood of abstinence from smoking for as long as one year compared to treatment with placebo

Accidental Injury, including while Driving, Operating Machinery
There have been post-marketing reports of traffic accidents, near-miss incidents in traffic, and other accidental injuries in patients taking CHAMPIX. In some cases, the patients reported somnolence, dizziness, loss of consciousness (blackouts), seizures or difficulty concentrating.

Therefore, patients should be advised not to engage in potentially hazardous activities, such as driving a car or operating dangerous machines, until they know how CHAMPIX may affect them.

Concomitant Illness The full consequences of using this product in patients with concomitant illness have not been studied, and caution should be exercised (see **Special Populations, Use of CHAMPIX in Patients with Concomitant Conditions)**.

Nicotine replacement therapy (NRT)
The concomitant use of NRT with CHAMPIX (varenicline tartrate) may result in an increase in adverse reactions. In a clinical drug interaction study (N=24), the incidences of nausea, headache, vomiting, dizziness, dyspepsia and fatigue were greater for the combination of NRT and varenicline than for NRT alone (see DRUG INTERACTIONS). The safety and efficacy of the combination treatment with CHAMPIX and NRT have not been studied. Due to the proposed mechanism of action of varenicline, it is not anticipated that co-administration with NRT would confer additional benefit compared with CHAMPIX alone.

Effect of smoking-cessation
Physiological changes resulting from smoking-cessation, with or without treatment with CHAMPIX, may alter the pharmacokinetics or pharmacodynamics of some drugs for which dosage adjustment may be necessary (examples include theophylline, warfarin and insulin). As smoking induces cytochrome P450 (CYP) isoenzyme 1A2, smoking-cessation may result in an increase of plasma levels of CYP1A2 substrates.

Nausea
Nausea was the most common adverse event associated with CHAMPIX treatment. Nausea was generally described as mild or moderate and often transient; however, for some subjects, it was persistent over several months. The incidence of nausea was dose-dependent. Initial dose-titration was beneficial in reducing the occurrence of nausea. Nausea was reported by approximately 30% of patients treated with CHAMPIX 1.0 mg BID after an initial week of dose titration. In patients taking CHAMPIX 0.5 mg BID, the incidence of nausea was 16% following initial titration. Approximately 3% of subjects treated with CHAMPIX 1.0 mg BID in studies involving 12 weeks of treatment discontinued treatment prematurely because of nausea. For patients with intolerable nausea, dose reduction should be considered (see **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment)**.

Carcinogenesis and Mutagenesis
For animal data, see **Part II**: **TOXICOLOGY** section.

Dependence/Tolerance

Animal Studies

The subjective nicotine-like effects of varenicline were investigated in drug discrimination studies. At 1.0 mg/kg, there was complete substitution of varenicline for nicotine in a paradigm of nicotine-associated lever pressing for food reward. In an efficacy model, varenicline pretreatment dose-dependently reduced nicotine self-administration under a fixed-ratio schedule. Under a progressive ratio schedule rats worked harder for nicotine than for varenicline.

Human Studies

The rewarding potential of varenicline (1 mg and 3 mg doses) was compared with that of amphetamines in subjects experienced with psychomotor stimulants. The pattern for both smokers and non-smokers was consistent with a profile of a drug that, while having some pharmacological activity, did not produce amphetamine-like subjective effects.

Patient Counselling Information

Consumer Information is included in the package of CHAMPIX dispensed to the patient.

Prior to prescribing CHAMPIX, physicians should:

- Discuss with the patient the expected benefits and risks of CHAMPIX, as well as those of all smoking-cessation options. In many cases, nicotine replacement therapy should be tried before prescribing CHAMPIX.
- Inform the patients that quitting smoking, with or without CHAMPIX, may be associated with nicotine withdrawal symptoms (including depression or agitation) or exacerbation of pre-existing psychiatric disorder.
- Advise patients not to engage in potentially hazardous tasks, such as driving a car or operating dangerous machines, until they know how CHAMPIX may affect them. In some cases, patients have reported somnolence, dizziness, loss of consciousness, seizures or difficulty concentrating while driving.
- Advise patients that some people have reported seizures while taking CHAMPIX and encourage them to report any history of seizures or other factors that can lower seizure threshold. Instruct patients to discontinue CHAMPIX and immediately contact a healthcare provider if they experience a seizure while on treatment.
- Inform the patient that there have been post-marketing reports of serious neuropsychiatric symptoms in patients being treated with CHAMPIX, including anxiety, psychosis, mood swings, aggression, depressed mood, agitation, hallucinations, hostility, changes in behavior or thinking, suicidal ideation, suicidal behavior and suicide, as well as worsening of pre-existing psychiatric disorder. These have occurred while taking CHAMPIX or shortly after discontinuing CHAMPIX.
- Inform the patient that these events have occurred in people with previous psychiatric disorder, as well as those with no previous history.
- Encourage the patient to reveal any history of psychiatric disorder prior to initiating treatment.
- Inform patients with a history of serious psychiatric disorder that there is limited information about the safety and efficacy of CHAMPIX in such patients.
- Inform patients with concomitant psychiatric conditions, even if well controlled, or with a

history of psychiatric symptoms, that if they are prescribed CHAMPIX, they will be diligently monitored by their physician for new or worsened psychiatric events.
- Inform patients that i) new or worse cardiovascular events (heart and stroke) have been reported, primarily in those who already have cardiovascular problems and ii) based on available data, it is not possible to determine whether CHAMPIX increases the risk of cardiovascular events.

Patients receiving CHAMPIX should be given the following instructions by the physician:

- Patients should be instructed to read the patient information leaflet supplied with every CHAMPIX prescription before starting their CHAMPIX pills. This leaflet is approved by Health Canada and is Part III of the CHAMPIX Product Monograph.
- Patients should also be provided with educational materials and necessary counselling to support an attempt at quitting smoking, including a review of the overall smoking cessation plan with the physician.
- Patients should call 1-800-CHAMPIX for a list of provincial Smoking Cessation resources (toll-free quit line) which can be used to support a quit attempt.
- Patients should be informed that there are two choices in setting a quit date when using CHAMPIX, and discuss with their physician which one is best for them.
- Patients should also be informed that there are two choices of CHAMPIX doses, based on physician judgment and patient preference: after one week titration, the dose can go up to 1.0 mg twice daily, or remain at 0.5 mg twice daily. Based on the limited data available, the two doses do not appear different in terms of either quit rates, or rates of serious psychiatric side effects (see **DOSAGE AND ADMINISTRATION, Dosing Considerations**).
- Patients should be instructed on how to titrate CHAMPIX, beginning at a dose of 0.5 mg per day. Prescribers should explain that one 0.5 mg tablet should be taken daily for the first three days, and that for the next four days, two 0.5 mg tablets should be taken daily: one in the morning and one in the evening.
- Following one week of titration, there are two dosing options: the dose can remain at 0.5 mg twice daily or can go up to 1.0 mg twice daily, depending on the dosing regimen chosen.
- Patients should be informed that the maximum dose of CHAMPIX is 1.0 mg twice a day.
- If needed, the dose can be changed depending on how well the patient tolerates CHAMPIX and how effective the doctor and patient consider it is in helping the patient quit smoking.
- Patients should be encouraged to continue in their quit attempt if they have early lapses after their quit date.
- Patients should be encouraged to inform friends and family members/caregivers of their quit attempt which includes treatment with CHAMPIX and ask for their support and help in monitoring for any changes in behavior or thinking that are not typical for the patient.
- Patients should be informed that if they develop agitation, hostility, depressed mood or changes in behavior or thinking that are not typical for them, or develop suicidal ideation or suicidal behavior, CHAMPIX should be discontinued immediately, and symptoms reported to their healthcare provider.

- Patients should be advised that drinking alcohol may increase the risk of experiencing psychiatric adverse events during treatment with CHAMPIX.
- Patients should be informed that they may experience vivid, unusual or strange dreams during treatment with CHAMPIX.
- Patients should be informed that nausea is the most common adverse event associated with CHAMPIX and is usually transient. CHAMPIX should be taken after eating and with a full glass of water. Patients should be advised that if they are persistently troubled by this symptom, a dose reduction may be considered.
- Patients should be informed that there have been reports of **angioedema,** with swelling of the face, mouth (tongue, lips and gums) and neck (pharynx and larynx) that can lead to life-threatening respiratory compromise. Patients should be instructed to discontinue CHAMPIX and seek immediate emergency medical attention if they experience these symptoms.
- Patients should be informed that **serious skin reactions**, such as Stevens-Johnson syndrome and erythema multiforme, were reported by some patients taking CHAMPIX. Patients should be advised to stop taking CHAMPIX at the first sign of rash with mucosal lesions or skin reaction and seek immediate emergency medical attention.
- Patients should be instructed to notify their healthcare providers of symptoms of new or worsening cardiovascular events and to seek immediate medical attention if they experience signs and symptoms of myocardial infarction or stroke.

Special Populations

Use of CHAMPIX in Patients with Concomitant Conditions:

Psychiatric Patients
Patients with certain serious psychiatric disorders such as schizophrenia, bipolar disorder, and major depressive disorder did not participate in the pre-marketing clinical trials of CHAMPIX. Smoking cessation studies subsequent to CHAMPIX marketing provided limited data in patients with stable schizophrenia or schizoaffective disorder, and in patients with major depressive disorder (See **ACTIONS AND CLINICAL PHARMACOLOGY, Study in Subjects with Stable Schizophrenia or Schizoaffective Disorder, Patients with Major Depressive Disorder).**

Smoking-cessation with or without pharmacotherapy, has been associated with the exacerbation of underlying psychiatric illness; the impact on this population of a smoking-cessation product with nicotinic partial agonist properties is unknown. Care should be taken with patients with a history of psychiatric illness and patients should be advised accordingly. **Patients with concomitant psychiatric conditions, even if well controlled, or with a history of psychiatric symptoms, should be diligently monitored by a healthcare professional for new or worsened psychiatric events** (see **WARNINGS AND PRECAUTIONS, Serious WARNINGS and PRECAUTIONS, and also Pre-existing Psychiatric Disorders or Symptoms).**

Patients with Epilepsy
The use of CHAMPIX has not been studied in patients with epilepsy. There have been post-marketing reports of seizures in patients using varenicline. It is not known for how many of these there is a prior history or risk of a seizure disorder (see **WARNINGS AND PRECAUTIONS, Seizures**).

Patients with Diabetes
Smoking cessation, with or without treatment, may be associated with altered glycemic control. There have been post-marketing reports of diabetic patients experiencing loss of glycemic control while taking CHAMPIX. Therefore, increased glycemic monitoring is recommended in diabetic patients, with resultant adjustment of diabetic medications as necessary.

Patients with Irritable Bowel or Other Gastrointestinal (GI) Problems
The use of CHAMPIX has not been studied in patients with irritable bowel syndrome or other GI problems. Post marketing reports of irritable bowel syndrome, abdominal pain, faecal incontinence and other GI issues have been reported in patients taking CHAMPIX.

Patients Exposed to Chemotherapy
The use of CHAMPIX has not been studied in patients exposed to emetogenic chemotherapy.

Pregnant Women
There are no adequate data from the use of CHAMPIX in pregnant women. Studies in animals have shown reproductive toxicity (see **TOXICOLOGY**). The potential risk for humans is unknown. CHAMPIX should not be used during pregnancy.

Nonteratogenic Effects
Varenicline succinate has been shown to have an adverse effect on the fetus in animal reproduction studies. Administration of varenicline succinate to pregnant rabbits resulted in reduced fetal weights at an oral dose of 30 mg/kg/day (50 times the human AUC at 1.0 mg BID); this reduction was not evident following treatment with 10 mg/kg/day (23 times the maximum recommended daily human exposure based on AUC). In addition, in the offspring of pregnant rats treated with varenicline succinate there were decreases in fertility and increases in auditory startle response at an oral dose of 15 mg/kg/day (36 times the maximum recommended human daily exposure based on AUC at 1.0 mg BID).

Nursing Women
Animal studies have shown that varenicline can be transferred to nursing pups. It is not known whether varenicline is excreted in human milk. Because many drugs are excreted in human milk and because the potential for adverse reactions in nursing infants from CHAMPIX is unknown, a decision should be made whether to discontinue nursing or to discontinue the drug.

Pediatrics (<18 years of age)
Safety and efficacy of CHAMPIX in pediatric patients have not been established; therefore, CHAMPIX is not recommended for use in patients under 18 years of age.

Geriatrics (>65 years of age)
A combined single and multiple-dose pharmacokinetic study demonstrated that the pharmacokinetics of 1.0 mg varenicline given once daily (QD) or BID 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 (see **DOSAGE AND ADMINISTRATION, Special Populations**: **Geriatrics**).

Renal Impairment
A multiple dose pharmacokinetic study was conducted in patients with normal renal function, with mild, moderate, or severe renal impairment (estimated creatinine clearance: >80 mL/min, >50 and ≤80 mL/min, ≥ 30 and ≤50 mL/min, and <30 mL/min, respectively) or end-stage renal disease (ESRD). Varenicline pharmacokinetics was unchanged in subjects with mild renal impairment. Relative to subjects with normal renal function, varenicline exposure increased 1.5-fold in patients with moderate renal impairment and 2.1-fold in patients with severe renal impairment. In subjects with ESRD, varenicline was efficiently removed by hemodialysis. The recommended dose of CHAMPIX is reduced in patients with severe renal impairment. CHAMPIX is not recommended in patients with ESRD **(s**ee **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions: Renal Impairment,** and **DOSAGE AND ADMINISTRATION, Special Populations: Patients with Impaired Renal Function).**

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Clinical Trial Adverse Drug Reactions

Smoking-cessation with or without treatment is associated with various symptoms. For example, dysphoric or depressed mood, insomnia, irritability, frustration or anger, anxiety, difficulty concentrating, restlessness, decreased heart rate, increased appetite or weight gain have been reported in patients attempting to stop smoking.

Overview
Pre-marketing clinical trials included approximately 2300 patients treated for at least 12 weeks, approximately 700 for 6 months, and approximately 100 for one year. In general, onset of adverse events was in the first few weeks of therapy and severity was generally mild to moderate. No differences were observed by age, race or gender with regard to the incidence of adverse reactions, although patient numbers in elderly, and in non-caucasian races were too limited to allow conclusions.

Commonly Observed Adverse Events
The most commonly observed adverse events associated with CHAMPIX (>5% and twice the rate seen in placebo-treated patients) were nausea, abnormal dreams, constipation, flatulence, and vomiting.

For patients exposed to the maximum recommended dose of 1.0 mg BID following initial dosage titration, the incidence of nausea was 30%, compared with 16% in 0.5 mg BID and approximately 10% in placebo-treated patients. Nausea was generally described as mild to moderate and often transient; however, for some subjects, it was persistent throughout the treatment period.

Adverse Events Leading to Discontinuation
In Phase 2 and 3 placebo-controlled studies, the treatment discontinuation rate due to adverse events in patients randomized to 12 weeks treatment with the recommended maximum dose of 1.0 mg BID was 12% for CHAMPIX compared to 10% for placebo. In this group, the adverse events most frequently resulting in treatment discontinuation in CHAMPIX treated patients were as follows: nausea (2.7% vs 0.6% for placebo), insomnia (1.3% vs 1.2% for placebo), fatigue/malaise/asthenia (1.0% vs 0.5% for placebo), and dizziness (0.7% vs 0.4% for placebo).

Table 1 shows the adverse events for CHAMPIX and placebo in the 12-week fixed dose studies with titration in the first week (Studies 1 (titrated arm only), 3, and 4). MedDRA High Level Group Terms (HLGT) reported in ≥5% of patients in the CHAMPIX 1.0 mg BID dose group, and more commonly than in the placebo group, are listed, along with subordinate Preferred Terms (PT) reported in ≥1% of CHAMPIX patients (and at least 0.5% more frequently than placebo). Closely related Preferred Terms such as 'Insomnia', 'Initial insomnia', 'Middle insomnia', 'Early morning awakening' were grouped, but individual patients reporting two or more grouped events were only counted once.

Table 1. Common Treatment Emergent Adverse Events (%) in the 12-Week Fixed-Dose, Placebo-Controlled Studies (≥ 1% in the 1.0 mg BID CHAMPIX Group, and 1.0 mg BID CHAMPIX at least 0.5% more than Placebo)

SYSTEM ORGAN CLASS HIGH LEVEL GROUP TERM Preferred Term	CHAMPIX 0.5 mg BID N=129	CHAMPIX 1.0 mg BID N=821	Placebo N=805
GASTROINTESTINAL			
GI 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			
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
RESPIR/THORACIC/MEDIAST			
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
Pruritus	0	1	1
METABOLISM & NUTRITION			
Appetite/General Nutrition 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

Initial dose titration was beneficial in reducing the occurrence of nausea.

An additional 12 weeks of CHAMPIX 1.0 mg BID was well-tolerated in patients who had completed 12 weeks of treatment and had stopped smoking. Adverse events resulted in treatment discontinuation in 1.7% of patients who received CHAMPIX compared with 1.3% of placebo patients.

Safety Study: One-Year, Double-Blind Drug-Treatment

The overall pattern and the frequency of adverse events during a 52-week trial with CHAMPIX 1.0 mg BID (n=251 subjects randomized to CHAMPIX arm, and n=126 to placebo arm) were similar to those described in Table 1, except for the following events which were seen to be increased relative to placebo, as compared to the profile for 12 week drug exposure: nausea (40% vs 8% placebo); and the pooled terms of: abdominal pain (17% vs 3% placebo), and increased blood pressure (11% vs 6% placebo). Few of these events were recorded as severe.

Neuropsychiatric Adverse Events in Randomized, Double-Blind, Placebo-Controlled Clinical Studies of Varenicline

Pooled Data including Ten Smoking Cessation Trials

Table 2 below provides the incidence of all causality, treatment-emergent neuropsychiatric adverse events with varenicline as compared to placebo (≥ 0.2% more than placebo) in adult smokers, adverse event summarized from all randomized, placebo-controlled, double-blind varenicline studies (10 studies) completed by 31 December 2008, regardless of Study Dose or Duration. Four of these are described in the CLINICAL TRIALS section. There were no suicidal and self-injurious behaviors reported (suicide ideation and suicide attempt) in the varenicline group versus 2 events (0.1%) in the placebo group.

Table 2: All-Causality Treatment-Emergent Neuropsychiatric Adverse Events (%) in Ten Completed Phase 2/4 Placebo-Controlled Studies (≥ 0.2% more than placebo).

Neuropsychiatric Adverse Events	**Varenicline** (N =3091)	**Placebo** (N =2005)
	% (n)	% (n)
Psychiatric Disorders*		
Depressed mood disorders and disturbances	**2.8 (88)**	**1.9 (38)**
Depression	1.6 (51)	1.2 (24)
Depressed mood	1.0 (32)	0.6 (12)
Disturbances in thinking and perception	**0.4 (13)**	**0.1 (2)**
Thinking abnormal	0.2 (7)	-- (1)
Mood disorders and disturbances NEC	**2.4 (73)**	**1.5 (30)**
Affect lability	0.6 (20)	0.3 (6)
Mood swings	0.3 (10)	0.1 (2)
Apathy	0.2 (5)	-- (1)
Psychiatric disorders NEC	**0.5 (16)**	**0.3 (6)**
Sleep disorders and disturbances	**25.1 (776)**	**14.5 (291)**
Insomnia	13.9 (431)	9.5 (191)
Abnormal dreams	9.9 (305)	3.6 (73)
Sleep disorder	3.1 (97)	1.7 (35)
Middle insomnia	1.1 (35)	0.3 (7)
Initial insomnia	1.0 (30)	0.6 (12)
Nightmare	0.5 (17)	0.3 (7)
Early morning awakening	0.4 (13)	0.1 (3)
Nervous System Disorders**		
Mental impairment disorders	**4.0 (124)**	**3.6 (73)**
Disturbance in attention	3.4(104)	3.1 (63)
Amnesia	0.3 (9)	0.1 (2)
Neurological disorders NEC	**16.4 (507)**	**13.0 (260)**
Dysgeusia	6.2 (193)	3.2 (64)
Somnolence	3.4 (105)	2.4 (49)
Lethargy	0.8 (25)	0.4 (8)

MedDRA version 11; included data up to 30 days after last dose of drug
NEC: Not Elsewhere Classified
Number (%) of Subjects with Adverse Events by:

*** Psychiatric Disorders System Organ Class: All High Level Group Terms (HLGT)** and Preferred Terms (PTs) reported in each HLGT that are ≥ 0.2 % greater than placebo.

**** Nervous System Disorder System Organ Class Selected HLGTs** and PTs reported in each HLGT that are ≥ 0.2 % greater than placebo.

Data from One Phase 2 Trial with Two Varenicline Doses

Data are shown from the Phase 2 trial (12 weeks duration) that included both efficacious doses, 0.5 mg BID and 1.0 mg BID (see **CLINICAL TRIALS**, **Study 1**).

Table 3: All-Causality Treatment-Emergent Neuropsychiatric Adverse Events (%) in one Phase 2 Dose Response Study that included both, 0.5 mg BID and 1.0 mg BID doses, (≥ 1% greater than placebo for any varenicline dose regimen).

Neuropsychiatric Adverse Events *	**0.5 mg BID (N= 253)**	**1.0 mg BID (N=253)**	**Placebo (N= 121)**
	% (n)	% (n)	% (n)
Total Psychiatric Disorders			
Depressed mood disorders and disturbances	**4.3 (11)**	**3.2 (8)**	**3.3 (4)**
Depressed mood	1.2 (3)	0.8 (2)	-- (0)
Disturbances in thinking and perception	**1.2 (3)**	**0.8 (2)**	**-- (0)**
Thinking abnormal	1.2 (3)	-- (0)	-- (0)
Mood disorders and disturbances NEC	**2.8 (7)**	**3.6 (9)**	**3.3 (4)**
Affect lability	0.8 (2)	2.0 (5)	0.8 (1)
Sexual dysfunction, disturbances and gender identity disorders	**0.4 (1)**	**1.6 (4)**	**-- (0)**
Libido decreased	-- (0)	1.6 (4)	-- (0)
Sleep disorders and disturbances	**34.4 (87)**	**36.4 (92)**	**15.7 (19)**
Insomnia	20.6 (52)	22.9 (58)	9.9 (12)
Abnormal dreams	12.6 (32)	18.2 (46)	4.1(5)
Sleep disorder	2.4 (6)	4.0 (10)	0.8 (1)
Initial insomnia	3.2 (8)	1.2 (3)	1.7 (2)
Early morning awakening	1.2 (3)	0.8 (2)	-- (0)
Nervous System Disorders**			
Mental impairment disorders	**6.3 (16)**	**9.9 (25)**	**4.1 (5)**
Disturbance in attention	5.9 (15)	7.9 (20)	4.1 (5)
Amnesia	-- (0)	1.2 (3)	-- (0)
Neurological disorders NEC	**22.9 (58)**	**24.9 (63)**	**14.0 (17)**
Dysgeusia	11.9 (30)	12.6 (32)	4.1 (5)
Somnolence	3.6 (9)	7.1 (18)	1.7 (2)
Lethargy	1.2 (3)	2.8 (7)	-- (0)
Hypoaesthesia	0.4 (1)	1.2 (3)	-- (0)

MedDRA version 11; included data up to 30 days after last dose of drug
NEC: Not Elsewhere Classified
Number (%) of Subjects with Adverse Events by:
*** Psychiatric Disorder System Organ Class: High Level Group Terms (HLGT)** and Preferred Terms (PT) reported in each HLGT ≥ 1% greater than placebo.
**** Nervous System Disorders System Organ Class:** Selected **HLGTs** and PTs reported in each HLGT ≥ 1% greater than placebo.

Additional Clinical Trial Adverse Drug Reactions

The adverse drug reactions listed below are based on evaluation of data from pre-marketing phase 2-3 studies and updated based on a pooled database of a total of 18 placebo-controlled, pre- and post-marketing smoking cessation studies, with approximately 5,000 patients treated with CHAMPIX. All reported events are included except those already listed in Table 1, those too general to be informative, and those not reasonably possibly associated with the use of the drug. In some cases, separate event terms have been consolidated to facilitate meaningful presentation. It is important to emphasize that although the events reported occurred during treatment with CHAMPIX, they were not necessarily caused by it.

The ADRs listed below are presented by the Medical Dictionary for Regulatory Activities (MedDRA, Version 16) System Organ Class (SOC). The variability associated with adverse event reporting and the terminology used to describe adverse events limit the value of the quantitative frequency estimates provided. Events are further classified within system organ class categories and enumerated in order of decreasing frequency using the following definitions: very frequent (occurring in at least 1/10 patients), frequent (occurring in at least 1/100 patients), infrequent (occurring in <1/100 to 1/1000 patients) and rare (occurring in fewer than 1/1000 patients).

Blood and Lymphatic System Disorders: ***Infrequent*****:** Anemia, Lymphadenopathy. ***Rare*****:** Leukocytosis, Platelet count decreased, Thrombocytopenia, Splenomegaly.

Cardiac Disorders: ***Infrequent:*** Angina pectoris, Electrocardiogram abnormal, Heart rate increased, Myocardial infarction, Palpitations, Tachycardia. ***Rare:*** Arrhythmia, Atrial fibrillation, Bradycardia, Cardiac flutter, Coronary artery disease, Cor pulmonale, Acute coronary syndrome, Electrocardiogram ST segment depression, Electrocardiogram T wave amplitude decreased, 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, Vision blurred, Visual-impairment, Eye pain. ***Rare:*** Acquired night blindness, Blindness transient, Cataract subcapsular, Dry eye, Mydriasis, Myopia, Lacrimation increased, Ocular vascular disorder, Photophobia, Scleral discolouration, Scotoma, Vitreous floaters.

Gastrointestinal Disorders: ***Frequent:*** Diarrhea, Toothache. ***Infrequent:*** Change of bowel habit, Aphthous stomatitis, Gingival pain, Dysphagia, Eructation, Gastritis, Gastrointestinal hemorrhage, Hematochezia, Mouth ulceration. ***Rare:*** Abnormal feces, Enterocolitis, Esophagitis, Gastric ulcer, Hematemesis, Intestinal obstruction, Pancreatitis acute, Tongue coated.

General Disorders and Administration Site Conditions: ***Frequent:*** Chest pain, Irritability. ***Infrequent:*** Chest discomfort, Chills, Edema, Influenza like illness, Pyrexia, Thirst. ***Rare:*** Cyst,

Feeling cold.

Hepatobiliary Disorders: ***Rare***: Gall bladder disorder, Worsening of existing autoimmune hepatitis.

Immune System Disorders: ***Infrequent:*** Hypersensitivity. ***Rare:*** Drug hypersensitivity.

Infections and Infestations: ***Very frequent*****:** Nasopharyngitis. ***Frequent*****:** Bronchitis, Sinusitis. ***Infrequent:*** Fungal infection, Gingivitis, Viral infection, Tooth abscess, Urinary Tract Infection.

Investigations: ***Frequent:*** Liver function test abnormal, alanine aminotransferase increased, ***Rare:*** Muscle enzyme increased, Semen abnormal, C-reactive protein increased, Blood calcium decreased, Urine analysis abnormal.

Metabolism and Nutrition Disorders: ***Frequent:*** Weight increased. ***Infrequent:*** Diabetes mellitus, Hypoglycemia. ***Rare:*** Hyperkalemia, Hyperlipidemia, Hypokalemia, Polydipsia.

Musculoskeletal and Connective Tissue Disorders: ***Frequent***: Arthralgia, Back pain, Myalgia. ***Infrequent:*** Arthritis, Musculoskeletal chest pain, Muscle cramp, Musculoskeletal pain, Muscle spasms. ***Rare:*** Costochondritis, Joint stiffness, Myositis, Osteoporosis.

Nervous System Disorders: ***Frequent:*** Disturbance in attention, Dizziness, Somnolence. ***Infrequent:*** Amnesia, Convulsion, Hypoesthesia, Migraine, Parosmia, Syncope, Tremor. ***Rare:*** Balance disorder, Cerebrovascular accident, Circadian rhythm sleep disorder, Coordination abnormal, Dysarthria, Hypertonia, Hypogeusia, 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: ***Frequent:*** Agitation, Anxiety, Depression. ***Infrequent:*** Aggression, Dissociation, Libido decreased, Libido increased, Mood swings, Panic reaction, Restlessness, Suicidal ideation, Thinking abnormal. ***Rare:*** Bradyphrenia, Disorientation, Dysphoria, Emotional disorder, Euphoric mood, Hallucination, Psychotic disorder, Suicide attempt.

Renal and Urinary Disorders: ***Infrequent:*** Nocturia, Pollakiuria, Urine abnormality. ***Rare:*** Glycosuria, Nephrolithiasis, Polyuria, Renal failure acute, Urethral syndrome, Urinary retention.

Reproductive System and Breast Disorders: ***Frequent:*** Menstrual disorder. ***Infrequent:*** Erectile dysfunction, Menorrhagia. ***Rare:*** Sexual dysfunction, Vaginal discharge.

Respiratory, Thoracic and Mediastinal Disorders: ***Frequent:***Cough, Respiratory disorders. ***Infrequent:*** Asthma, Dysphonia, Epistaxis, Rhinitis allergic, Throat irritation, Respiratory tract congestion, Sinus congestion, Rhinorrhea, Upper-airway cough syndrome, Upper respiratory tract inflammation. ***Rare:*** Laryngeal pain, Pleurisy, Pulmonary embolism, Snoring.

Skin and Subcutaneous Tissue Disorders: ***Frequent:*** Rash. ***Infrequent:*** Acne, Dry skin, Eczema, Erythema, Hyperhidrosis, Night sweats, Urticaria. ***Rare:*** Dermatitis, Photosensitivity reaction, Psoriasis.

Vascular Disorders: ***Frequent:*** Hypertension. ***Infrequent:*** Blood pressure increased, Hot flush, Hypotension. ***Rare:*** Peripheral ischemia, Thrombosis.

Clinical Trials in Special Populations

Adverse Events in Adolescents: (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Pediatrics**).

Cardiovascular Adverse Events in Pooled Clinical Studies of Varenicline

In pooled data of 14 completed randomized double-blind placebo controlled smoking cessation trials (not including the study in patients with stable cardiovascular disease), the rate of reported treatment-emergent myocardial infarction (MI) or cerebrovascular accident (CVA) related adverse events was: 8 of 3317 (0.24%) patients on CHAMPIX (>1 mg), compared to 4 of 2542 (0.16%) patients on placebo.

Study in patients with Cardiovascular Disease

CHAMPIX was evaluated in a randomized, double-blind, placebo-controlled study of 703 subjects aged 35 to 75 years with stable, documented cardiovascular disease (other than or in addition to hypertension) that had been diagnosed for more than 2 months. Patients were treated with CHAMPIX 1 mg BID or placebo for 12 weeks, and then followed for another 40 weeks post-treatment (See **WARNINGS AND PRECAUTIONS, Cardiovascular Events**).

There are two partially overlapping data sets of cardiovascular events from the study:

i) Treatment-emergent CV AEs captured via standard clinical trial AE reporting, while on drug treatment, (including, 30 days post-dose); and
ii) Pre-specified serious CV events that were adjudicated by an independent blinded committee captured throughout the 52 week duration (ie both "on-treatment" [including 30 days post-dose], and "post-treatment").

The study was powered for assessing efficacy (ie quit rates) but not for assessing differences in the occurrence of serious CV events between CHAMPIX and placebo.

More cardiovascular events were reported in both arms compared to other studies, as expected due to underlying conditions.

Treatment-emergent cardiovascular events which occurred within 30 days after the last dose, and in at least 3 subjects in either arm, are shown in **Table 4**.

Table 4: Treatment-Emergent Cardiovascular Events that occurred within 30 days after the last dose and in at least 3 subjects in any treatment arm

Cardiovascular Adverse Events	Varenicline (N = 353)	Placebo (N = 350)
	n (%)	n (%)
Angina pectoris	13 (3.7)	7 (2.0)
Chest pain	9 (2.5)	8 (2.3)
Peripheral edema	7 (2.0)	4 (1.1)
Arteriosclerosis	3 (0.8)	0 (0)
Hypertension	5 (1.4)	9 (2.6)
Palpitations	2 (0.6)	4 (1.1)

The adjudicated serious cardiovascular events are shown below in **Table 5**.

Patients are counted only once within each row per study phase.

As shown in **Table 5**, the individual serious cardiovascular (CV) events that were reported more frequently in CHAMPIX compared to placebo (difference > 2 subjects) were: non-fatal myocardial infarctions (4 vs. 1, on-treatment phase) and need for coronary revascularization (7 vs. 2, post-treatment phase). Some of the patients requiring coronary revascularization underwent the procedure as part of management of nonfatal MI and hospitalization for angina.

Table 5: Summary of Adjudicated Cardiovascular Events (including CV death) over the 52 Weeks of the Study

	Varenicline N=353			Placebo N = 350		
	Study Treatment Phase	**Study Post-Treatment Follow-Up Phase**	**Total Study Duration (52 Weeks)**	**Study Treatment Phase**	**Study Post-Treatment Follow-Up Phase**	**Total Study Duration (52 Weeks)**
	Number of subjects with CV event, n (%)					
# of subjects with at least 1 CV event (including CV death)	10 (2.8)	16 (4.5)	25 (7.1)	9 (2.6)	11 (3.1)	20 (5.7)
Types of CV Events						
Nonfatal myocardial infarction	4 (1.1)	3 (0.8)[a]	7 (2.0)	1 (0.3)	2 (0.6)[b]	3 (0.9)
Need for coronary revascularization	1 (0.3)	7 (2.0)[a]	8 (2.3)	1 (0.3)	2 (0.6)	3 (0.9)
Hospitalization for angina pectoris	2 (0.6)	6 (1.7)	8 (2.3)	4 (1.1)	4 (1.1)[a]	8 (2.3)
Hospitalization for congestive heart failure	0 (0)	0 (0)	0 (0)	2 (0.6)	0 (0)	2 (0.6)
Nonfatal stroke	2 (0.6)	0 (0)	2 (0.6)	0 (0)	1 (0.3)	1 (0.3)
Transient ischemic attack	0 (0)	1 (0.3)	1 (0.3)	1 (0.3)	0 (0)	1 (0.3)
New diagnosis of peripheral vascular disease (PVD) or admission for a procedure for the treatment of PVD	1 (0.3)	5 (1.4)	5 (1.4)	1 (0.3)	2 (0.6)	3 (0.9)
Cardiovascular death	0 (0)	1 (0.3)[a]	1 (0.3)	1 (0.3)	1 (0.3)	2 (0.6)

[a] one of the events occurred while the subject was taking during the post treatment phase "off-protocol" CHAMPIX or [b] CHAMPIX and other smoking cessation medication.

CHAMPIX was not studied in patients with unstable cardiovascular disease or those with cardiovascular events occurring within two months before screening. (See also: **WARNINGS AND PRECAUTIONS, Cardiovascular Events, and ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions)**

Post-Marketing Experience

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

Psychiatric Symptoms
There have been reports of depressed mood, agitation, aggression, hostility, anxiety, changes in behavior or thinking, mania, psychosis, hallucinations, paranoia, delusions, homicidal ideation, mood swings, suicidal ideation and completed suicide in patients attempting to quit smoking while taking CHAMPIX (see **WARNINGS AND PRECAUTIONS, Psychiatric Symptoms**). Of the cases with information provided, the majority reported possible contributing factors, including primarily prior psychiatric history and/or concurrent psychiatric medications. Smoking status at the time of event onset was not reported in most cases. Patients should be advised that alcohol intake may increase the risk of experiencing psychiatric adverse events. Smoking cessation with or without treatment is associated with nicotine withdrawal symptoms and the exacerbation of underlying psychiatric illness. The role of CHAMPIX in these reports is not known (see also **WARNINGS AND PRECAUTIONS**, **Psychiatric Symptoms**).

Hypersensitivity and Serious Skin Reactions
There have also been reports of hypersensitivity reactions, including angioedema and of rare but severe cutaneous reactions including Stevens-Johnson syndrome and erythema multiforme in patients taking CHAMPIX (see **WARNINGS AND PRECAUTIONS, Angioedema and Hypersensitivity Reactions** and **Serious Skin Reactions**).

Myocardial Infarction and Cerebrovascular Accident
There have been reports of myocardial infarction (MI) and cerebrovascular accident (CVA) including ischemic and hemorrhagic events in patients taking Champix. In the majority of the reported cases, patients had preexisting cardiovascular disease and/or other risk factors. Although smoking is a risk factor for MI and CVA, a contributory role of varenicline cannot be ruled out, based on temporal relationship between medication use and events.

Hyperglycemia and Diabetes Mellitus
Smoking cessation, with or without treatment, may be associated with altered glycemic control. There have been reports of hyperglycemia in patients taking CHAMPIX. While the majority of these cases involved diabetic patients experiencing loss of glycemic control (see **Special Populations**, **Patients with Diabetes)**, there have also been reports of new onset diabetes in patients with no pre-existing diabetes or pre-diabetes.

DRUG INTERACTIONS

Overview

Based on varenicline pharmacokinetic characteristics, and clinical experience to date, it appears unlikely that CHAMPIX would produce or be subject to clinically meaningful drug interactions.

Drug interaction studies were performed with varenicline and: cimetidine, metformin, digoxin, warfarin, transdermal nicotine and bupropion.

No clinically meaningful pharmacokinetic drug interactions have been identified, other than

potential for interaction with cimetidine in patients with severe renal impairment (see ***Cimetidine***, below).

Drugs cleared by, or which affect, cytochrome P450 enzymes
In vitro studies demonstrated that varenicline does not inhibit cytochrome P450 enzymes (IC50 >6400 ng/mL). The P450 enzymes tested for inhibition were: 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4/5. Also, in human hepatocytes *in vitro*, varenicline did not induce the activity of cytochrome P450 enzymes 1A2 and 3A4. Therefore, varenicline is unlikely to alter the pharmacokinetics of compounds that are primarily metabolized by cytochrome P450 enzymes.

Furthermore, since metabolism of varenicline represents less than 10% of its clearance, drugs known to affect the cytochrome P450 system are unlikely to alter the pharmacokinetics of CHAMPIX (see **ACTION AND CLINICAL PHARMACOLOGY: Pharmacokinetics**) and therefore a dose adjustment of CHAMPIX should not be required for these types of drugs.

Drugs cleared by, or which affect, renal secretion
In vitro studies demonstrated that varenicline does not inhibit human renal transport proteins at therapeutic concentrations. Therefore, drugs that are cleared by renal secretion (eg, metformin - see below) are unlikely to be affected by varenicline.

In vitro studies demonstrated the active renal secretion of varenicline is mediated by the human organic cation transporter, hOCT2. In patients with normal renal function coadministration with inhibitors of hOCT2 does not require a dose adjustment of CHAMPIX as the increase in systemic exposure to CHAMPIX is not expected to be clinically meaningful except in cases of severe renal impairment (see ***Cimetidine***, and ***Other Inhibitors of hOCT2*** below).

Drug-Drug Interactions

Alcohol
See **Serious WARNINGS and PRECAUTIONS**; see also Patient Counselling Information.

Drug-drug interaction studies were limited to approximately two-week studies in healthy young adult volunteers who smoked.

Single dosing for one of the two drugs:

Cimetidine: Co-administration of varenicline (2 mg single dose) with an hOCT2 inhibitor, cimetidine (300 mg four times daily (QID) at steady-state) to 12 smokers increased the systemic exposure of varenicline by 29% (90% CI: 21.5%, 36.9%) due to a reduction in varenicline renal clearance. No dosage adjustment is recommended based on concomitant cimetidine administration in subjects with normal renal function or in patients with mild to moderate renal impairment. In patients with severe renal impairment, the concomitant use of cimetidine and varenicline should be avoided (see **DOSAGE AND ADMINISTRATION**, **Recommended Dose and Dosage Adjustment: Special Populations,** ***Patients with Impaired Renal Function***).

Other inhibitors of hOCT2: Other inhibitors of hOCT2 have not been directly studied. Cimetidine causes greater *in vivo* drug interactions with renally cleared compounds than other inhibitors of hOCT2. Consequently, co-administration of other inhibitors of hOCT2 with varenicline would not require dosage adjustment in patients with normal renal function or moderate renal impairment. In patients with severe renal impairment, the concomitant use of varenicline and other inhibitors of hOCT2, such as trimethoprim, ranitidine or levofloxacin should be avoided (see **DOSAGE AND ADMINISTRATION**, **Recommended Dose and Dosage Adjustment: Special Populations,** ***Patients with Impaired Renal Function***).

Co-administration with Other Drugs Eliminated via hOCT2*:* Based on the lack of interaction between varenicline and metformin, interactions between varenicline and other cationic drugs eliminated via hOCT2 are unlikely.

Warfarin: Varenicline (1 mg BID steady-state) did not alter the pharmacokinetics of a single 25 mg dose of (R, S)-warfarin in 24 smokers. Prothrombin time (INR) was not affected by CHAMPIX. Smoking-cessation itself may result in changes to warfarin pharmacokinetics (see **WARNINGS AND PRECAUTIONS**).

Multiple dosing for both drugs:

Metformin: When co-administered to 30 smokers, varenicline (1 mg BID) did not alter the steady-state pharmacokinetics of metformin (500 mg BID), which is a substrate of hOCT2. Metformin had no effect on varenicline steady-state pharmacokinetics.

Digoxin: Varenicline (1 mg BID) did not alter the steady-state pharmacokinetics of digoxin administered as a 0.25 mg daily dose in 18 smokers. Steady-state pharmacokinetics of varenicline remained unchanged by digoxin co-administration.

***Use with other therapies for smoking-cessation*:**

Safety and efficacy of varenicline in combination with other smoking-cessation therapies, such as bupropion or nicotine replacement therapy, have not been studied.

Bupropion: Varenicline (1 mg BID) did not alter the steady-state pharmacokinetics of bupropion (150 mg BID) in 46 smokers. Steady-state pharmacokinetics of varenicline remained unchanged by bupropion co-administration.

Nicotine replacement therapy (NRT): When varenicline (1 mg BID) and NRT (transdermal, 21 mg/day) were co-administered to 24 smokers for 12 days, there was a statistically significant decrease in average systolic blood pressure (mean 2.6 mmHg) measured on the final day of the study. In this study, the incidence of nausea, headache, vomiting, dizziness, dyspepsia and fatigue were greater for the combination of varenicline and NRT than for NRT alone. Due to the partial agonist nicotinic activity of varenicline, it is not anticipated that co-administration with NRT would confer additional benefits compared with CHAMPIX alone, and may result in increased side effects (see **WARNINGS AND PRECAUTIONS**).

Drug-Food Interactions
Oral bioavailability of CHAMPIX is unaffected by food.

Drug-Herb Interactions
CHAMPIX has no known drug-herb interactions.

Drug-Laboratory Interactions
CHAMPIX has no known drug-laboratory test interactions.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Prior to a decision to prescribe non-nicotine treatment including CHAMPIX, thorough consideration should be given to the treatment option of nicotine replacement therapy.

Smoking-cessation therapies are more likely to succeed for patients who are motivated to stop smoking and who are provided additional counseling and /or support services. In the clinical trials on which approval was based, CHAMPIX was used with supportive counseling. Physicians should review the patient's overall smoking-cessation plan that includes treatment with CHAMPIX.

The majority of clinical evidence in efficacy and safety was based on a 1.0 mg BID dose (see **CLINICAL TRIALS**). There is little clinical experience with doses above the maximum recommended dose of 1 mg BID.

There is limited data available for dose comparison. In the one randomized clinical trial that included both 1.0 mg BID and 0.5 mg BID arms and that was designed to compare each of the two doses to placebo, and not to each other, the quit rates for 1.0 mg BID (n=253), 0.5 mg BID (n=253) and placebo (n=121) were:

- for Weeks 9 to 12: 51%, 45%, and 12% respectively, and
- for Weeks 9 to 52: 23%, 19% and 4% respectively.

For further information on this study, see CLINICAL TRIAL, study 1.

Based on the limited data available, it cannot be concluded that there is a difference between the two doses in the rate of serious neuropsychiatric events (see **ADVERSE REACTIONS, Neuropsychiatric Adverse Events in Randomized Double Blind, Placebo Controlled Clinical Studies of Varenicline**).

CHAMPIX should be taken after eating and with a full glass of water.

Patients with Impaired Renal Function
For patients with severe renal impairment, daily dosage should be adjusted accordingly (see **Recommended Dose and Dosage Adjustment: Special Populations,** ***Patients with Impaired Renal Function***, below).

Recommended Dose and Dosage Adjustment
Adults

Setting a Quit Date

There are two ways to set a quit date with CHAMPIX:

- The patient sets a date to stop smoking. CHAMPIX dosing should start 1-2 Weeks before this date.

  or

- The patient begins CHAMPIX and then quits smoking between days 8 and 35 of treatment (ie between Weeks 2 and 5) (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations, Flexibility in Setting a Quit Date**).

Regardless of the approach to setting a quit date, dosing instructions are the same (as below)

Dosing Options

Following one week of titration, there is a choice of two doses for CHAMPIX: 0.5 mg BID or 1.0 mg BID.

As shown in the table below, the two titration schedules are identical from Day 1 to Day 7, separating at Day 8 when the patient either remains on 0.5 mg BID or moves up to 1.0 mg BID.

Day	Dosing regimen	
	0.5 mg BID	1.0 mg BID
Days 1 – 3:	0.5 mg once daily	0.5 mg once daily
Days 4 – 7:	0.5 mg twice daily	0.5 mg twice daily
Day 8 – onward	0.5 mg twice daily	1.0 mg twice daily

The choice of dosing regimen should be based on physician judgment and patient preference, following discussion with the patient (see also **Dosing Considerations**).

Once CHAMPIX treatment is initiated, the dose may be changed, temporarily or permanently, according to patient and physician judgments on tolerability and efficacy.

Patients should be treated with CHAMPIX for 12 weeks. For patients who have successfully stopped smoking at the end of 12 weeks, an additional course of 12 weeks treatment with CHAMPIX may be considered. No data are available on the efficacy of an additional 12 week

course of treatment with CHAMPIX for patients who have not successfully stopped smoking at the end of 12 weeks.

Dose tapering may be considered. Regardless of whether the treatment course is 12 or 24 weeks, risk of smoking-cessation relapse is elevated in the period immediately following the end of drug treatment (see **CLINICAL TRIALS***)*. In addition, dose tapering may help minimize discontinuation symptoms (eg, increase in irritability, urge to smoke, depression, and/or insomnia), observed in up to 3% of patients at the end of treatment.

Special Populations

Patients with Impaired Renal Function:
No dosage adjustment is necessary for patients with mild (estimated creatinine clearance >50 mL/min and ≤ 80 mL/min) to moderate (estimated creatinine clearance ≥ 30 mL/min and ≤50 mL/min) renal impairment. For patients who experience intolerable adverse events, dosing may be reduced.

For patients with severe renal impairment, the recommended dose of CHAMPIX is 0.5 mg twice daily. Dosing should begin at 0.5 mg once daily for the first 3 days then increased to 0.5 mg twice daily. Based on insufficient clinical experience with CHAMPIX in patients with end-stage renal disease, treatment is not recommended in this patient population (see also **WARNINGS AND PRECAUTIONS, Special Populations: Renal Impairment**).

Patients with Hepatic Impairment:
No dosage adjustment is necessary for patients with hepatic impairment.

Psychiatric Patients, Patients with Epilepsy, Patients undergoing Chemotherapy, and Patients with GI disturbances such as irritable bowel: The use of CHAMPIX has not been studied in these patient populations (see **WARNINGS AND PRECAUTIONS, Special Populations**).

Dosing in Elderly Patients:
No dosage adjustment is necessary for elderly patients with normal renal function. However, 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 (see **WARNINGS AND PRECAUTIONS**, **Special Populations: Geriatrics**).

Use in Children:
Safety and effectiveness of CHAMPIX in pediatric patients have not been established; therefore, CHAMPIX is not recommended for use in patients under 18 years of age.

OVERDOSAGE

Symptoms
Consistent with its pharmacological profile, CHAMPIX resulted in increased incidences of nausea and vomiting when given at doses greater than the recommended dose of 1 mg BID.

Treatment
Varenicline has been shown to be dialyzed in patients with end-stage renal disease (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions: Renal Insufficiency**), however, there is no experience with dialysis following overdose.

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

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

The efficacy of CHAMPIX in smoking-cessation is believed to be a result of varenicline's partial agonist activity at the α4β2 nicotinic acetylcholine receptor (ie, agonist activity to a lesser degree than nicotine), while simultaneously preventing nicotine binding (ie, antagonist activity).

In vitro, varenicline binds with higher affinity to the α4β2 receptor subtype than to other common nicotinic receptors (>500-fold α3β4; >3,500-fold α7; >20,000-fold α1βγδ), or to non-nicotinic receptors and transporters (> 2,000-fold).

Electrophysiology studies *in vitro* and neurochemical studies *in vivo* have shown that varenicline acts as a partial agonist at α4β2 nicotinic acetylcholine receptors. In the absence of nicotine, varenicline's agonist activity is at a significantly lower level than nicotine, but sufficient to activate the central nervous mesolimbic dopamine system, believed to be the neuronal mechanism underlying reinforcement and reward experienced upon smoking. In the presence of nicotine, which competes for the same human α4β2 nicotinic acetylcholine receptor (nAChR) binding site, varenicline prevented nicotine from activating the α4β2 receptor, since it has higher affinity for this site and this prevented full stimulation of the central nervous mesolimbic dopamine system.

Varenicline is also a partial agonist at α3β4 receptors, but a full agonist at α7 receptors and a full agonist at 5-HT3 receptors.

Varenicline has moderate affinity for the 5-HT3 serotonergic receptor (Ki=350 nM), at which it acts as a weak, full agonist (EC50=0.96 μM). Varenicline-induced nausea shortly after dosing, when gastrointestinal levels are predicted to be temporarily high, may be due to activation of this peripheral receptor, in addition to a possible role for peripheral α3β4 and/or central α4β2 nAChRs.

Pharmacokinetics

Table 6. Summary of Mean with Standard Deviation Varenicline Pharmacokinetic Parameters in Adult Male and Female Smokers

	C_{max} (ng/mL)	T_{max}[b] (hr)	AUC_{0-24} (ng·h/mL)	$t_{½}$ (hr)	Clearance[c] (L/hr)	Volume of distribution[c] (L)
1.0 mg [a] BID	9.22 (2.05)	3.00 [1.00-8.00]	194[†] (42.7)	33.0[‡] (14.4)	10.4 (25%CV)	337 (50%CV)

[a]Derived from three multiple-dose studies (N=103); [†]N=64; [‡]N=46
[b]T_{max} presented as median [range]
[c]Apparent clearance and central volume of distribution estimated from a population PK analysis conducted on pooled data from 1878 subjects (49.2% females); presented as typical value (interindividual coefficient of variation)

Absorption: Maximum plasma concentrations of varenicline occur typically within 3-4 hours after oral administration. Following administration of multiple oral doses of varenicline to healthy volunteers, steady-state conditions were reached within 4 days. Varenicline exhibits linear kinetics when given as single (0.1 to 3 mg) or repeated (1 to 3 mg/day) doses.
In a mass balance study, absorption of varenicline is virtually complete after oral administration and systemic availability is high. Oral bioavailability of varenicline is unaffected by food or time-of-day dosing.

Distribution: Plasma protein binding of varenicline is low (≤20%) and independent of both age and renal function.

Metabolism: Varenicline tartrate undergoes minimal metabolism, with approximately 92% of recovered drug-related entity in urine being unchanged varenicline. Metabolite profiles (for circulation and urine) were similar for smokers and non-smokers, and are from the following minor routes of metabolism: N-carbomyl glucuronidation, N-formylation and conjugation with a hexose sugar.

Elimination: The elimination half-life of varenicline tartrate is approximately 24 hours. Renal elimination of varenicline is the major elimination route, primarily through glomerular filtration along with active tubular secretion via the organic cationic transporter, OCT2.

Special Populations and Conditions

There were no clinically meaningful differences seen in varenicline tartrate pharmacokinetics due to being elderly, race, gender, smoking status, or use of concomitant medications, as demonstrated in specific pharmacokinetic studies and in population pharmacokinetic analyses.

Pediatrics: Two pharmacokinetic studies have been conducted in adolescent smokers, aged 12-17 inclusive: a single dose study (n= 27), and a multiple dose study (n= 72). Pharmacokinetics were approximately dose-proportional over the 0.5 mg to 2 mg daily dose range studied.

Steady-state systemic exposure: In the multiple-dose study, patients were stratified by bodyweight (> 55 kg; ≤ 55 kg), and within each bodyweight group, were randomized into three treatment arms (low dose of varenicline, high dose of varenicline and placebo) using a 2:2:1 randomization scheme. Dosing was as follows:

- >55 kg: 0.5 mg BID (n = 14), 1.0 mg BID (n = 14) and placebo (n = 7);
- ≤ 55 kg 0.5 mg QD (n = 15), 0.5 mg BID (n = 14) and placebo (n= 8).

The dosing period was 14 days, with all arms at target dose by Day 8. Patients were allowed to continue smoking at will throughout the study.

In adolescent patients of bodyweight >55 kg, steady-state systemic exposures, as assessed by AUC (0-24), were consistent with those previously observed in the adult population. In adolescent patients of ≤ 55 kg, steady-state systemic exposure for the 0.5 mg BID was on average approximately 40% higher compared to that previously observed in the adult population.

Individual adverse event terms (MedDRA-coded preferred terms) that were reported in more than one patient taking CHAMPIX and more frequently than for placebo were: nausea (most frequent), headache, vomiting, dizziness, pharyngolaryngeal pain, abdominal pain upper, anorexia, flatulence, abnormal dreams, arthralgia, fatigue, and somnolence. Patients ≤55 kg reported more adverse events than patients > 55 kg.

Mood-related events were reported for three patients of 57 in the CHAMPIX arms (anger, mood swings, irritability; none severe), compared with 0 reports in 15 patients in the placebo arms.

Because the safety and effectiveness of varenicline in pediatric patients have not been established, varenicline is not recommended for use in patients under 18 years of age.

Geriatrics: A combined single and multiple-dose pharmacokinetic study demonstrated that the pharmacokinetics of 1 mg varenicline given once 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.

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 (see **DOSAGE AND ADMINISTRATION, Special Populations**: **Dosing in Elderly Patients**).

Hepatic Insufficiency: Due to the absence of significant hepatic metabolism, varenicline tartrate pharmacokinetics should be unaffected in patients with hepatic insufficiency, except in the case that there is accompanying renal compromise (see **DOSAGE AND ADMINISTRATION**). The potential for clinically meaningful drug interactions between varenicline and metabolic inhibitors/inducers is low.

Renal Impairment: Varenicline tartrate pharmacokinetics were studied in subjects with normal, mild, moderate, severe renal impairment and end-stage renal disease (n=6 per arm), following 0.5 mg once daily administration for 12 days.

Varenicline pharmacokinetics were essentially unchanged in subjects with mild renal impairment (estimated creatinine clearance >50 mL/min and ≤80 mL/min).

In patients with moderate renal impairment (estimated creatinine clearance ≥30 mL/min and ≤50 mL/min), varenicline exposure [AUCτ] increased 1.5-fold compared with subjects with normal renal function (estimated creatinine clearance >80 mL/min).

In subjects with severe renal impairment (estimated creatinine clearance <30 mL/min), varenicline exposure [AUCτ] was increased 2.1-fold.

In subjects with end-stage renal disease (ESRD), undergoing a three-hour session of hemodialysis for three days a week, varenicline exposure [AUCτ] was increased 2.7-fold; varenicline was efficiently removed by hemodialysis (see **DOSAGE AND ADMINISTRATION**, **Recommended Dose and Dosage Adjustment: Special Populations,** ***Patients with Impaired Renal Function***).

Patients with Cardiovascular Disease
CHAMPIX was evaluated in a randomized, double-blind, placebo-controlled smoking cessation study of subjects aged 35 to 75 years with stable, documented cardiovascular disease (other than or in addition to hypertension) that had been diagnosed for >2 months. Subjects were randomized to CHAMPIX 1 mg BID (n=353) or placebo (n=350) for 12 weeks of treatment and then were followed for 40 weeks post-treatment. Quit rates were in the range of those from studies in the general population of smokers. Adverse events in this study were quantitatively and qualitatively similar to those observed in studies in the general population of smokers, other than cardiovascular-related events (see also **WARNINGS AND PRECAUTIONS, Cardiovascular Events**).

Patients with Chronic Obstructive Pulmonary Disease
CHAMPIX was evaluated in a randomized, double-blind, placebo-controlled smoking cessation study of 499 subjects with mild-to-moderate COPD with post-bronchodilator FEV1/FVC<70% and FEV_1 ≥50% of predicted normal value, aged > 35 years. Subjects were randomized and treated with CHAMPIX 1 mg BID (n=248) or placebo (n=251) for 12 weeks and then followed for 40 weeks post-treatment. Quit rates were in the range of those from studies in the general population of smokers. Adverse events in this one-year study were quantitatively and qualitatively similar to those observed in studies in the general population of smokers.

Patients with Stable Schizophrenia or Schizoaffective Disorder
CHAMPIX safety and tolerability was assessed in a double-blind study of 128 smokers with stable schizophrenia or schizoaffective disorder, on antipsychotic medication, randomized 2:1 to varenicline (1 mg twice daily) or placebo for 12 weeks with 12-week non-drug follow-up.

Assessments including the Positive and Negative Symptom Scale (PANSS), standard questioning regarding adverse events, and the Columbia Suicide Severity Rating Scale (C-SSRS) occurred weekly through week 13 and at weeks 16, 20 and 24.

Based on adverse event rates, including neuropsychiatric, there were no new safety concerns compared to studies in the general population of smokers. The study discontinuation rate due to neuropsychiatric adverse events in the CHAMPIX arm was 4% (3 /84), compared to 0 (0 /43) in the placebo group.

In this study, there was no overall worsening of schizophrenia in either treatment group as measured by PANSS scores nor worsening of extra-pyramidal signs.

Evaluation of suicidal ideation and behavior (including C-SSRS): Reported lifetime history of suicidality was higher in the patients randomized to the CHAMPIX arm compared to placebo [62% (52 /84) and 51% (22/43) respectively]. During the active treatment period, the rate of C-SSRS endorsement was 11% (9/82) in the CHAMPIX arm and 9% (4/43) in the placebo arm. There were two suicide-related actions by two patients treated with CHAMPIX (attempt through overdose, and preparatory act of collecting pills); both patients had a lifetime history of similar behaviours.

During the 12 week post-treatment phase, the rate of C-SSRS endorsement decreased in the placebo arm to 5% (2/39), while the rate in the CHAMPIX arm remained at 11% (8 / 70). For six of the cases, all in the CHAMPIX arm, the C-SSRS endorsements were the first in the study for those individuals and occurred more than 30 days after last treatment dose.

All incidences of suicidal ideation or behavior during the study, except for one patient treated with CHAMPIX, occurred in patients with a prior history of suicidality.

The limited data available from this single smoking cessation study are not sufficient to allow for definitive conclusions to be drawn about the safety of CHAMPIX in patients with schizophrenia or schizoaffective disorder (see also **WARNINGS AND PRECAUTIONS, Pre-existing Psychiatric Disorder or Symptoms).**

Patients with Major Depressive Disorder
CHAMPIX was evaluated in a randomized, double-blind, placebo-controlled study of 525 subjects with major depressive disorder without psychotic features (DSM-IV TR), on stable antidepressant treatment and/or who experienced a major depressive episode (which was successfully treated) in the past 2 years. Subjects aged 18 to 75 years were randomized to CHAMPIX 1 mg BID (n=256) or placebo (n=269) for a treatment of 12 weeks and then followed for 40 weeks post-treatment. Quit rates in this study were in the range of those from studies in the general population of smokers.

In general, the adverse events in this one-year study were quantitatively and qualitatively similar to those observed in studies in the general population of smokers.

The following psychiatric AEs were more frequent in the CHAMPIX group vs placebo: agitation (6.6% vs. 4.1%), depression (6.6% vs. 4.8%), tension (3.5% vs. 3.0%), hostility (2.0% vs. 0.4%) and restlessness (2.0% vs. 1.9%). No overall worsening of depression was observed during the study in neither CHAMPIX or placebo treatment groups.

The percentage of subjects with suicidal ideation and/or behavior during treatment were 6.0% and 7.5% respectively for the CHAMPIX and placebo groups and 6.2% vs 5.8% for the non-treatment follow-up period. There was one event of intentional self-injury/possible suicide attempt during treatment (Day 73) in a subject with history of alcohol abuse in the placebo group. A possible 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 CHAMPIX group.

Flexibility in Setting a Quit Date
CHAMPIX was evaluated in a double-blind, placebo-controlled study where patients were instructed to select a quit date between the start of Week 2 of treatment (Day 8) and the end of Week 5 (Day 35) of treatment. It was not required that the quit date be selected prior to starting treatment. Subjects were randomized 3:1 and treated for 12 weeks with CHAMPIX 1 mg BID (n=486) or placebo (n=165) and followed for another 12 weeks post-treatment. Quit rates were in the range of those from studies with a fixed target quit date.

Patients Re-treated with CHAMPIX
CHAMPIX was evaluated in a double-blind, placebo-controlled trial of 494 patients who had made a previous attempt to quit smoking with CHAMPIX, and either did not succeed in quitting or relapsed after treatment. Subjects were randomized 1:1 to CHAMPIX 1 mg BID (n=249) or placebo (n=245) for 12 weeks of treatment and followed for up to 40 weeks post-treatment. Patients included in this study had taken CHAMPIX for a smoking-cessation attempt in the past (for a total treatment duration of a minimum of two weeks), at least three months prior to study entry, and had been smoking for at least four weeks. Quit rates in this study were in the range of those from studies in subjects at their first attempt to quit smoking with CHAMPIX.

Adverse events in this one-year study were quantitatively and qualitatively similar to those from studies in subjects at their first attempt to quit with CHAMPIX.

STORAGE AND STABILITY

Store at room temperature (15–30ºC).

DOSAGE FORMS, COMPOSITION AND PACKAGING

CHAMPIX is supplied for oral administration in two strengths:

0.5 mg: capsular biconvex, white to off-white, film-coated tablet debossed with "*Pfizer*" on one side and "CHX 0.5" on the other side. Each tablet contains 0.5 mg of varenicline (as tartrate). Supplied in high-density polyethylene (HDPE) bottles of 56 tablets and in packs containing blister strips of 11 tablets.

1.0 mg: capsular biconvex, light blue film-coated tablet debossed with "*Pfizer*" on one side and "CHX 1.0" on the other side. Each tablet contains 1.0 mg of varenicline (as tartrate). Supplied in high-density polyethylene (HDPE) bottles of 56 tablets and in packs containing blister strips of 14 or 28 tablets.

Initial dosing pack: Includes one blister containing both 11 x 0.5 mg and 14 x 1.0 mg tablets and a second blister of 28 x 1.0 mg tablets.

Nonmedicinal ingredients are microcrystalline cellulose, anhydrous dibasic calcium phosphate, croscarmellose sodium, colloidal silicon dioxide and magnesium stearate. The film-coating contains hypromellose, titanium dioxide, polyethylene glycol and triacetin. The 1.0 mg tablet also contains FD&C Blue #2/Indigo Carmine Aluminum Lake as a colouring agent.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

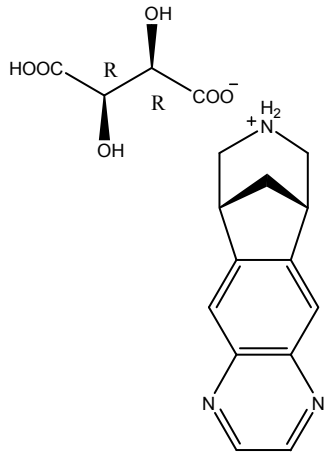
Proper name : Varenicline tartrate

Chemical name: 7,8,9,10-tetrahydro-6,10-methano-6*H*-pyrazino[2,3-*h*][3]benzazepine, (2*R*,3*R*)-2,3-dihydroxybutanedioate (1:1)

Molecular formula: $C_{13}H_{13}N_3 \bullet C_4H_6O_6$

Molecular weight: 361.35 Daltons

Structural formula:



Physicochemical properties: Varenicline tartrate powder is a white to off-white to slightly yellow solid which is highly soluble in water.

CLINICAL TRIALS

The efficacy of CHAMPIX (varenicline tartrate) in smoking-cessation was demonstrated in five double-blind, placebo-controlled clinical trials in which a total of 4190 chronic cigarette smokers (about 10 cigarettes per day) received varenicline. Patients set a date to stop smoking (target quit date, or TQD) of 1 week after treatment initiation. For four of the studies, the primary outcome was based on 12 weeks of drug treatment, with a subsequent 40 weeks of double-blind assessment, post drug-treatment. Of these four, two included a bupropion SR arm. The fifth study assessed the effect of 12 weeks of double-blind treatment on maintenance of abstinence achieved during a prior 12 weeks of open-label varenicline.

The four smoking cessation studies with 12 weeks treatment:

Primary objective: A comparison of varenicline to placebo, and additionally in each of the two studies with a bupropion SR arm comparison of varenicline (1 mg BID) to buproprion SR.

Primary endpoint: Abstinence Responder rate was defined as % of patients for whom 4-week continuous abstinence from Week 9 through Week 12 (4 Week-Continuous Quit Rate, or 4W-CQR) was recorded. Abstinence from smoking was determined on a weekly basis, by patient self-report and measurement of expired carbon monoxide levels (CO). Abstinence was defined as self-report of not even a puff of a cigarette, and by having CO measurements of ≤ 10 ppm. Intent-to-treat population was used, and patients who discontinued drug treatment early were eligible as responders, provided they chose to remain in the study.

Key secondary endpoint: Continuous Abstinence Rate (CAR) was defined as the proportion of all patients who reported that they did not smoke (not even a puff of a cigarette) from Week 9 through to Week 52 (ie, including the 40-week, non-drug treatment period), and had an exhaled CO measurement of ≤10 ppm.

Study 1; 12-week randomized dose comparison:
This study compared CHAMPIX 0.5 mg BID (n=253) and 1.0 mg BID (n=253) with placebo (n=121). Each treatment arm had two different regimens - with or without a week of dose titration – in order to explore the effect on tolerability. The titrated and non-titrated groups were pooled for efficacy analysis.

Study 2; 12-week flexible dose study:
This study (n=312) examined the effect of patient-directed dosing strategy of CHAMPIX or placebo. After an initial one week titration to a dose 0.5 mg BID, patients could adjust their dosage as often as they wished between 0.5 mg QD to 1.0 mg BID. Sixty-nine percent (69%) of patients titrated to the maximum allowable dose at any time during the study. For 44% of patients, the modal dose selected was 1.0 mg BID; for 52% of the study patients, the modal dose selected was 1.0 mg/day or less.

Study 3 and Study 4; Identical 12-week studies with active comparator arm:
Two identical double-blinded clinical trials prospectively compared the efficacy of CHAMPIX (1.0 mg BID) to placebo, and to sustained release bupropion (150 mg BID) in the absence of

NRT in smoking-cessation. Patients received treatment for 12 weeks and then were followed for a total study duration of 52 weeks. The CHAMPIX dosage of 1.0 mg BID was achieved using a titration of 0.5 mg once daily for the initial 3 days followed by 0.5 mg BID for the next 4 days. The bupropion dosage of 150 mg BID was achieved using a 3-day titration of 150 mg once daily.

Study Results

Primary Endpoint

In all four studies, the primary endpoint for CHAMPIX (ie, 4W-CQR from Week 9 to Week 12) demonstrated statistical superiority to placebo and in the subset of the two identical studies, statistical superiority to bupropion SR was also demonstrated with CHAMPIX 1.0 mg BID dose. No patients were allowed to use NRT during the drug treatment phase, and those who did were considered treatment failures. The 4W-CQR (weeks 9-12) for all four studies are shown in Table 7.

Table 7. Continuous Quit Rate, Week 9 through 12 across different studies

Studies	CHAMPIX 0.5 mg BID	CHAMPIX 1.0 mg BID	CHAMPIX Flexible	Bupropion SR	Placebo
Study 1	45%* n=253	51%* n=253			12% n=121
Study 2			40%* n=157		12% n=155
Study 3		44%*# n=349		30%†a n=329	17% n=344
Study 4		44%*# n=343		30%†a n=340	18% n=340

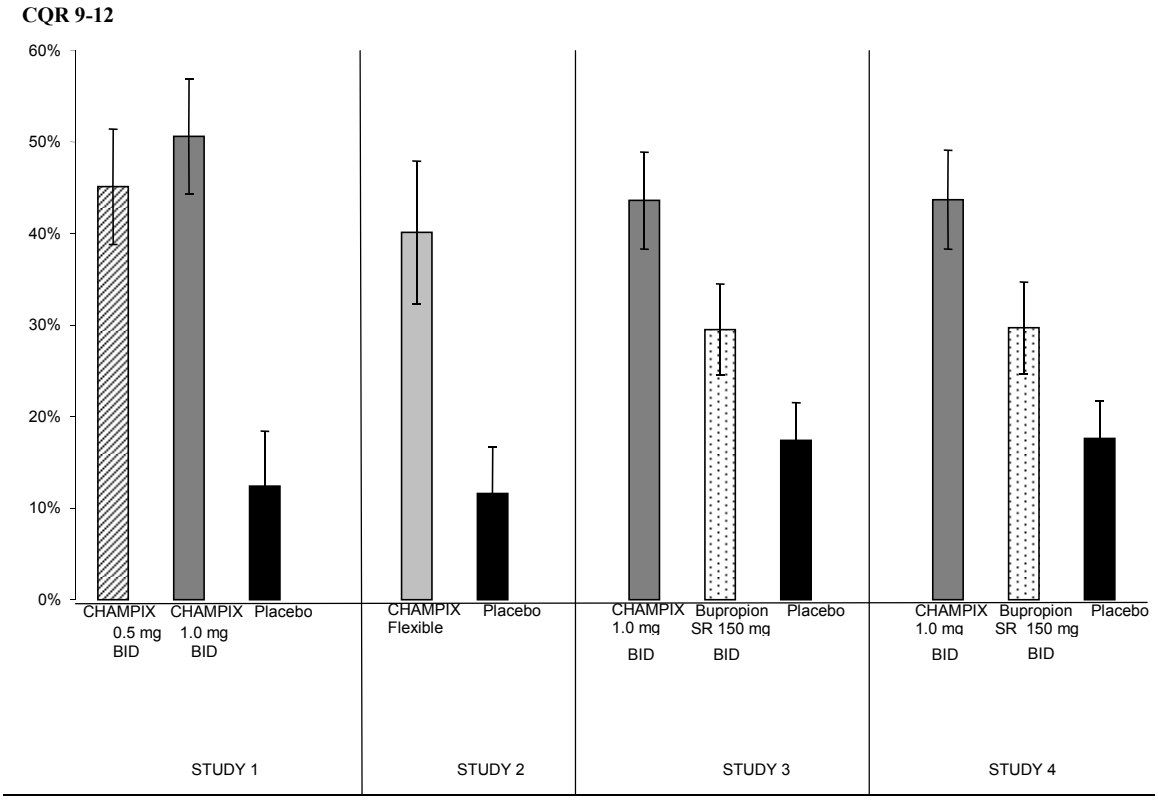
* P<0.0001 CHAMPIX vs placebo

† P<0.001 Bupropion SR vs placebo

# P<0.0001 CHAMPIX 1.0 mg BID vs Bupropion SR

[a] Statistical comparison of bupropion SR vs placebo was not protocol-specified.

Figure 1. Continuous Quit Rate, Week 9 through 12 across different studies



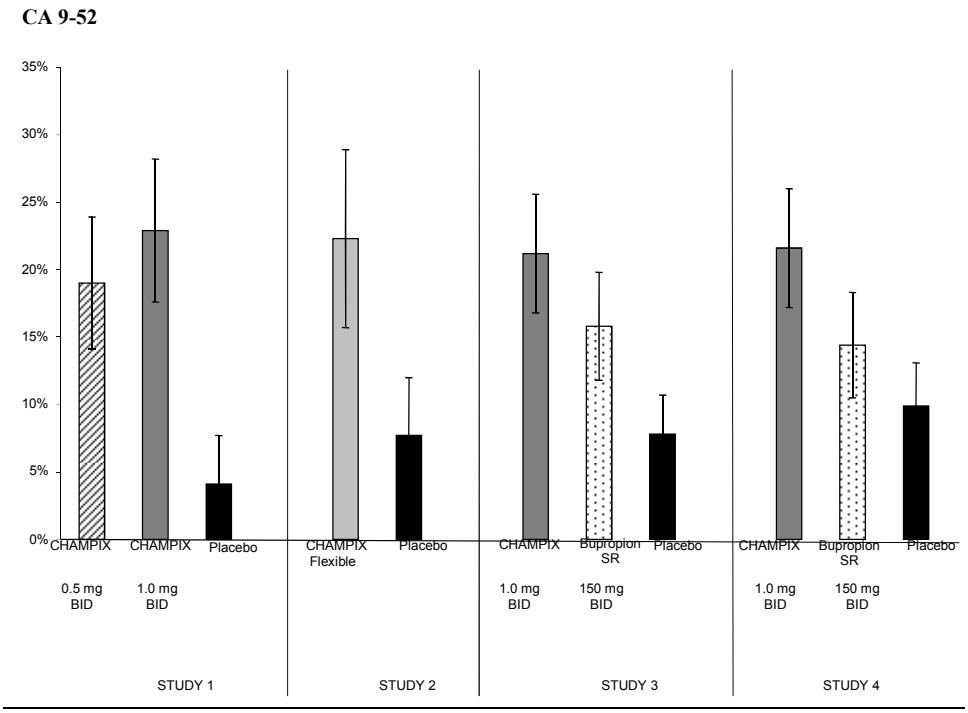
Secondary Endpoints:
In all four studies, a key secondary endpoint for CHAMPIX (ie, CAR Week 9 through 52) demonstrated statistical superiority to placebo. The CAR Weeks 9 through 52 for all four studies are shown in Table 8.

Table 8. Continuous Abstinence Rate, Week 9 through 52 across different studies

Studies	CHAMPIX 0.5 mg BID	CHAMPIX 1.0 mg BID	CHAMPIX Flexible	Bupropion SR	Placebo
Study 1	19%* n=253	22.9%* n=253			4.1% n=121
Study 2			22.3%* n=157		7.7% n=155
Study 3		22.1%* n=349		16.4%† [a] n=329	8.4% n=344
Study 4		23%* n=343		15% [a] n=340	10.3% n=340

* P<0.0001 CHAMPIX vs placebo
† P<0.001 Bupropion SR vs placebo
[a] Statistical comparison of bupropion SR vs placebo was not protocol-specified.

Figure 2. Continuous Abstinence Rate, Week 9 through 52 across different studies



Urge to Smoke and Withdrawal Symptoms
Based on the responses to the Brief Questionnaire of Smoking Urges and the Minnesota Nicotine Withdrawal Scale, as measured in the 12-week treatment period, craving and urge to smoke were significantly reduced in patients randomized to CHAMPIX compared to those randomized to placebo, as were negative affect withdrawal symptoms (depressed mood; irritability, frustration, or anger; anxiety; difficulty concentrating).

Maintenance of Abstinence Study
The fifth study assessed the benefit of an additional 12 weeks of CHAMPIX therapy on the maintenance of abstinence. Patients received open-label CHAMPIX 1.0 mg BID for 12 weeks. Patients who were abstinent for 7 continuous days at Week 12 were then randomized to double-blind treatment with either CHAMPIX (1.0 mg BID, n=602) or placebo (n=604) for an additional 12 weeks, and then followed for a total study duration of 52 weeks.

The primary study endpoint was the CO-confirmed-CAR (defined as above) from Week 13 through Week 24 in the double-blind treatment phase. A key secondary endpoint-was the CAR for Week 13 through Week 52.

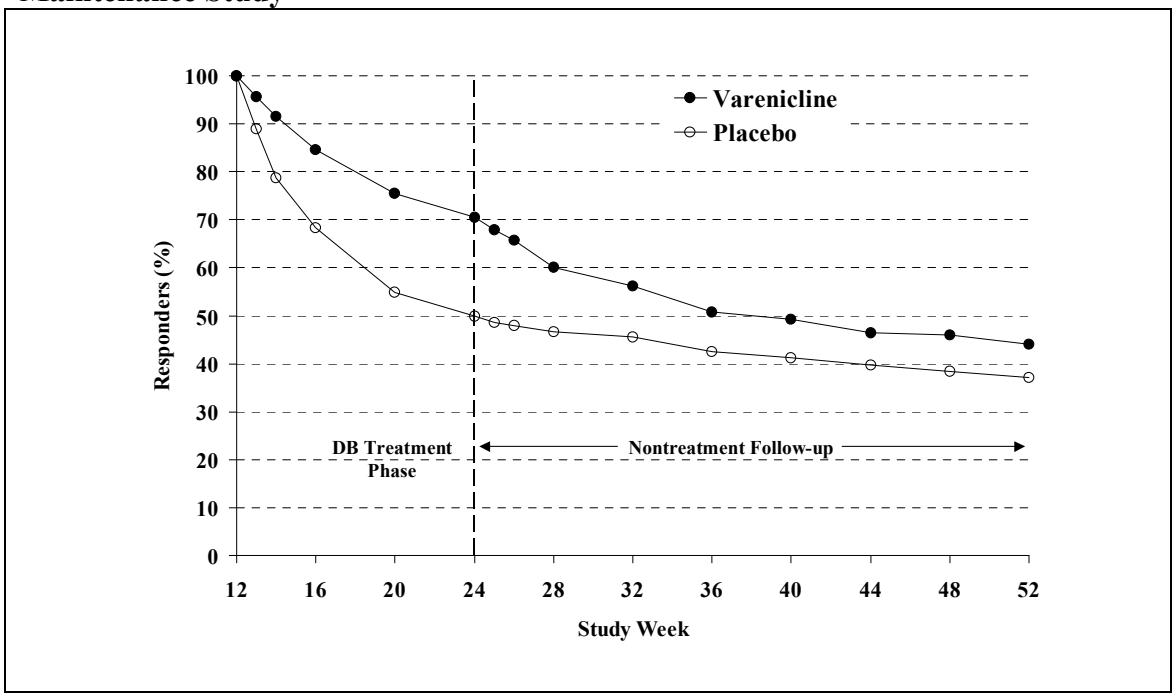
Superiority to placebo was shown for both the primary and secondary endpoints (see Table 9). The CAR from Week 13 through Week 24 was higher for patients continuing treatment with CHAMPIX (70.6%) than for patients switching to placebo (49.8%). Superiority to placebo was also maintained during the 28-week, post-treatment follow-up (CHAMPIX 44.0% versus placebo 37.1% at Week 52). This study showed the benefit of an additional 12 weeks of treatment with CHAMPIX 1.0 mg BID for the maintenance of smoking-cessation, compared to placebo. A statistically significant difference was maintained at Week 52, the final week of the study.

Table 9. Maintenance Study Results

	CHAMPIX N=602 (%)	Placebo N=604 (%)
CAR wk 13-24	70.6*	49.8
CAR wk 13-52	44.0**	37.1

* P<0.0001 CHAMPIX vs placebo
** P<0.01 CHAMPIX vs placebo
(CAR) continuous abstinence rate

Figure 3. Continuous Abstinence Rate from Week 13 through Week 52 Maintenance Study



Note: Subjects at Week 12 were those who were abstinent during the last week of open-label varenicline treatment and were randomized and received treatment in the double-blind phase.

DETAILED PHARMACOLOGY

Preclinical Pharmacology

In vitro and *in vivo* experiments demonstrate that varenicline performs as expected for a partial agonist of the α4β2 nicotinic receptor subtype. For example, dopamine turnover and microdialysis results in rats demonstrate that varenicline has a reduced ability to activate the mesolimbic dopamine system relative to nicotine, and in fact varenicline can attenuate the activating effects of nicotine on this system. While varenicline does substitute for nicotine in a discrimination paradigm, varenicline was shown to be less reinforcing than nicotine in rats trained to self-administer nicotine, and pretreatment with varenicline significantly decreased nicotine self-administration. Finally, in a withdrawal study in rats and a study assessing withdrawal in monkeys there were no observed behaviors or responses consistent with withdrawal effects.

In vivo and *in vitro* data demonstrate that varenicline is well absorbed after oral administration. Protein binding of varenicline is low and similar across species. It readily distributes throughout the body with increased but reversible association with melanin-containing tissues. Varenicline was shown to not interact with major human drug metabolizing CYPs. A substantial portion (75% - 93% of dose) of varenicline was excreted as unchanged drug in all species examined, with most drug-related material excreted in urine. Metabolites were minor and those observed in

human circulation and excreta were also observed in one or more animal species. *In vitro* data suggest that renal excretion of varenicline occurs by both passive filtration and an active transport process (likely via renal transporter OCT2).

TOXICOLOGY

The toxicology program was conducted to characterize the toxicity and dose response in the appropriate nonclinical species of the rat and monkey. No evidence of any unique toxicity or adverse pharmacological effects of varenicline in the expected range of human plasma exposure was observed in animals.

Acute and Repeated-Dose Toxicity

The toxicology program was conducted to characterize the toxicity and dose response in the appropriate nonclinical species of the rat and monkey. Effects were seen primarily in the gastrointestinal tract and the central nervous system (CNS) ie, tremors and convulsions at exposure multiples greater than those observed in humans. These changes were reversible.

Acute Toxicity

Acute oral studies in rat (30, 100, 200, and 300 mg/kg) and monkey (3 mg/kg) and intravenous (IV) studies in monkeys (0.08-0.3 mg/kg) were conducted.

In the single-dose study in rats, the findings were in the gastrointestinal system (decreased body weight and loose stool) and CNS (tremors and convulsions). The onset of the CNS clinical signs was rapid and occurred immediately to 2.5 hours post-dosing. All findings were reversed by the end of the 14-day observation period. There was one death in rats dosed at 300 mg/kg PO, a dose associated with exposure approximately 300-fold above expected human exposure.

The single-dose no observed adverse effect level (NOAEL) in monkeys was 0.2 mg/kg (0.1 mg/kg BID) corresponding to an exposure of approximately 1.2-fold above expected human exposure. In a single-dose oral study in monkeys at 3 mg/kg, the findings were also in the gastrointestinal system (emesis) and CNS (tremors). In addition electrocardiogram changes (decreased HR and QT interval and increased PRQ and P wave) were observed. Clinical signs (emesis and tremors) occurred at similar exposures after both oral gavage and IV dosing, both associated with exposure approximately 2- to 4-fold above expected human exposure. All of the findings occurred within ~1-4 hours post-dosing and were not present the next day.

Repeated-Dose Toxicity

Table 10. Repeat-Dose Gavage Pivotal Studies in Rats and Monkeys

Species	Duration	Dose (mg/kg/day)
Rats		
	6 Weeks	0.3, 3, 30
	3 Months	3, 10, 30
	6 Months	3, 10, 30
Monkeys		
	6 Weeks	0.01, 0.05, 0.2 (0.1 BID)
	3 Months	0.01, 0.05, 0.2 (0.1 BID)
	9 Months	0.01, 0.05, 0.2 (0.1 BID)
	9 Months	0.2 (0.1 BID), 0.4 (0.2 BID), 1.2 (0.6 BID)

Rats:
The no-observed adverse effect level (NOAEL) in rats was 10 mg/kg/day in the 3- and 6-month studies, which corresponds to C_{max} and AUC values that are 68 and 50 times those at the maximum recommended human dose (MRHD), respectively. The NOAELs in both studies were based on decreases in body weight and food consumption, which were attributed to decreases in gastric motility.

In the 6-week and 3-month rat studies at 30 mg/kg/day (associated with exposures of approximately 75- to 140-fold above expected human exposure) the findings were in the gastrointestinal tract; decreases in body weight, food consumption, and intestinal dilatation, which were consistent with decreases in gastric motility. At ≥ 10 mg/kg/day (associated with exposures of approximately 40- to 65-fold above expected human exposure), there were slight increases in alkaline phosphatase (ALP), alanine transaminase (ALT), and/or total bilirubin. In addition, hepatocellular single-cell necrosis was observed in a 10 day study, at 100 mg/kg/day. At ≥30 mg/kg/day, there were slight increases in hematocrit and hemoglobin. Similar changes were seen in mice and other rat studies, but not monkeys. The changes may be secondary to stress of decreased food consumption and dehydration.

In the 6-month rat study, findings were also in the gastrointestinal tract (decreases in body weight and food consumption). In this study, there were no biologically meaningful hepatic changes as compared to the marginal hepatic findings observed in the shorter-term studies.

Monkeys:
The NOAEL in cynomolgus monkeys was 0.2 mg/kg/day (0.1 mg/kg BID) in the first 9-month study. There were also no findings in the second 9-month study at this dose, which was the low dose. The next dose up (0.4 mg/kg/day) showed sporadic emesis and loose stools. The C_{max} and AUC at 0.2 mg/kg/day in monkeys was approximately 3-fold the human exposure at MRHD.

There were no findings in the 6-week, 3-month, or the first 9-month study, at doses up to 0.2 mg/kg/day.

In the second 9-month monkey study, the main finding at 0.4 mg/kg/day (0.2 mg/kg BID) was sporadic emesis. One female monkey was found dead at this dose of megacolon, secondary to

colonic torsion and ischemic necrosis. Megacolon is an uncommon spontaneous finding in monkeys. This finding was likely secondary to the gastrointestinal dysfunction (loose stools) that was evident prior to and during treatment, although drug treatment cannot be excluded. Colonic torsion was not observed in other monkeys with equivalent or higher doses. At 1.2 mg/kg/day (0.6 mg/kg BID) – approximately 10- to 12-fold above expected human exposure – all animals were euthanized or removed from study after 3-8 weeks of treatment due to body weight loss (>15% in 10 of 12 monkeys) associated with emesis and decreased food consumption. Decreases in core body temperature of 1-2 degrees Celcius were observed (and had also been seen in an earlier monkey study at 0.6 mg/kg/day, and were also seen in mice; body temperature perturbation is a well-known effect of nicotine). There were no treatment-related microscopic findings in any of the animals. Dosing was discontinued and the surviving animals at 1.2 mg/kg/day (0.6 mg/kg BID) were monitored for ~1 month. The clinical signs ceased and body weight returned to pretreatment levels within a month.

Carcinogenesis: Lifetime carcinogenicity studies were performed in CD-1 mice and Sprague-Dawley rats. There was no evidence of a carcinogenic effect in mice administered varenicline by oral gavage for 2 years at doses up to 20 mg/kg/day (47 times the maximum recommended human daily exposure based on the area under the curve (AUC). Rats were administered varenicline (1, 5, and 15 mg/kg/day) by oral gavage for 2 years. In male rats (n=65 per sex per dose group), incidences of hibernoma (tumor of the brown fat) was increased at the mid dose (1 tumor, 5 mg/kg/day, 23 times the maximum recommended human daily exposure based on AUC) and at the maximum dose (2 tumors, 15 mg/kg/day, 67 times the maximum recommended human daily exposure based on AUC). The clinical relevance of this finding to humans has not been established. There was no evidence of carcinogenicity in female rats.

Mutagenesis: Varenicline was not genotoxic, with or without metabolic activation, in the following assays: Ames bacterial mutation assay; mammalian CHO/HGPRT assay; and tests for cytogenetic aberrations *in vivo* in rat bone marrow and *in vitro* in human lymphocytes.

Sexual Function / Reproduction

Impairment of Fertility: There was no evidence of impairment of fertility in either male or female Sprague-Dawley rats administered varenicline succinate up to 15 mg/kg/day (67 and 36 times, respectively, the maximum recommended human daily exposure based on AUC at 1.0 mg BID). However, a decrease in fertility was noted in the offspring of pregnant rats who were administered varenicline succinate at an oral dose of 15 mg/kg/day (36 times the maximum recommended human daily exposure based on AUC at 1.0 mg BID). This decrease in fertility in the offspring of treated female rats was not evident at an oral dose of 3 mg/kg/day (9 times the maximum recommended human daily exposure based on AUC at 1.0 mg BID).

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PART III: CONSUMER INFORMATION
Pr CHAMPIX®
(varenicline tartrate tablets)

Read this information each time you refill your prescription in case new information has been added.

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

What is the most important information I should know about CHAMPIX?
Some people have had changes in behavior, hostility, agitation, aggression, depressed mood, and suicidal thoughts or actions while taking CHAMPIX to help them quit smoking.

These psychiatric symptoms have occurred in people with previous mental health issues, as well as in those with no previous history.

Some people had these symptoms when they began taking CHAMPIX, and others developed them after several weeks of treatment or after stopping CHAMPIX.

If you, your family, or caregiver notice agitation, hostility, depression or changes in behavior or thinking that are not typical for you, or you develop any of the following symptoms, stop taking CHAMPIX and call your healthcare provider right away:

- thoughts about suicide or dying, or attempts to commit suicide
- new or worse depression, anxiety or panic attacks
- feeling very agitated or restless
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- abnormal thoughts or sensations
- seeing or hearing things that are not there (hallucinations)
- feeling people are against you (paranoia)
- feeling confused
- other unusual changes in behavior

When you try to quit smoking, with or without CHAMPIX, you may have symptoms that may be due to nicotine withdrawal, including urge to smoke, depressed mood, trouble sleeping, irritability, frustration, anger, feeling anxious, difficulty concentrating, restlessness, decreased heart rate, and increased appetite or weight gain. Some people have even experienced suicidal thoughts when trying to quit smoking without medication. Sometimes quitting smoking can lead to worsening of mental health problems that you already have, such as depression.

Before taking CHAMPIX, tell your doctor if you have ever had depression or other mental health problems. You should also tell your doctor about any symptoms you had during other times you tried to quit smoking, with or without CHAMPIX. See "**SIDE EFFECTS AND WHAT TO DO ABOUT THEM**".

Some people can have allergic reactions to CHAMPIX. Some of these allergic reactions can be life-threatening and include: swelling of the face, mouth, and throat that can cause trouble breathing. If you have these symptoms, stop taking CHAMPIX and seek immediate emergency medical attention.

Some people can have serious skin reactions while taking CHAMPIX. These can include rash, swelling, redness, and peeling of the skin. Some of these reactions can become life-threatening. If you have a rash with peeling skin or blisters in your mouth, around the eyes or genitals, stop taking CHAMPIX and seek immediate emergency medical attention.

ABOUT THIS MEDICATION

What the medication is used for:
CHAMPIX is a prescription medicine which is used in combination with supportive counselling to help motivated adults stop smoking. In many cases, nicotine replacement therapy (patches, gum, lozenges, etc.) should be tried before trying CHAMPIX.

What it does:
CHAMPIX can help to relieve the craving and withdrawal symptoms associated with stopping smoking.

CHAMPIX does not contain nicotine, but it has been shown to affect the nicotine receptor in the brain that is thought to be most related to smoking addiction. CHAMPIX can affect this receptor in two opposite ways: it acts like a weaker version of nicotine, and also blocks

nicotine from getting to the receptor because it binds more tightly. Although it is thought that this may be, in part, how CHAMPIX works, it is not known exactly how the drug works in people. **When it should not be used:**

Do not take CHAMPIX

- If you are allergic (hypersensitive) to varenicline tartrate or any of the other ingredients of CHAMPIX (see list below of non-medicinal ingredients).
- If you are using nicotine replacement therapy, such as patches, gum or inhaler. The combination of CHAMPIX and nicotine replacement therapy is not expected to improve your chances of quitting, and may result in more side effects than with CHAMPIX alone.

What the medicinal ingredient is:

Varenicline tartrate.

What the nonmedicinal ingredients are:

The nonmedicinal ingredients are microcrystalline cellulose, anhydrous dibasic calcium phosphate, croscarmellose sodium, colloidal silicon dioxide and magnesium stearate. The film-coating contains hypromellose, titanium dioxide, polyethylene glycol and triacetin. The 1 mg tablet also contains FD&C Blue #2/Indigo Carmine Aluminum Lake as a colouring agent.

What dosage forms it comes in:

CHAMPIX is available as film-coated tablets. The 0.5 mg tablets are white and the 1 mg tablets are light blue.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Some people have had changes in behavior, hostility, agitation, aggression, depressed mood, and suicidal thoughts or actions while taking CHAMPIX to help them quit smoking. Some people developed them within days or weeks of starting CHAMPIX, or after stopping taking the drug.
- These psychiatric symptoms have occurred in people with previous mental health issues, as well as in those with no previous history.
- For more information on this, go to the section at the front of this leaflet "**What is the most important information I should know about CHAMPIX**".
- Be sure to have a discussion with your doctor about the risks and benefits of all options, including CHAMPIX, before deciding whether to start CHAMPIX.
- If you experience emotional, behavioral or psychiatric changes that are unusual for you while on CHAMPIX, stop taking the drug right away, and talk to your doctor.
- Drinking alcohol may increase the risk of experiencing psychiatric events during your treatment with CHAMPIX.
- You are encouraged to inform friends and family members of your quit attempt which includes treatment with CHAMPIX and ask for their support and help in monitoring for potential psychiatric symptoms.

BEFORE you use CHAMPIX talk to your doctor or pharmacist if:

- You have experienced depression or any other mental health problems. There is limited information about the use of CHAMPIX in people with mental health problems and therefore your doctor will monitor you closely for new or worsened emotional or behavioral problems during treatment with CHAMPIX.
- You have any problems with your kidneys, as you may need a lower dose of CHAMPIX.
- You have heart or blood vessel (cardiovascular) problems.
- You have a history of seizures
- You have any other medical conditions.

- You are pregnant, are breastfeeding or plan to become pregnant (see "Pregnancy" and "Breastfeeding" below).
- You have diabetes. CHAMPIX can potentially affect your blood sugar regulation, and you may need to monitor your blood sugar more often. If you notice changes, discuss this with your doctor.

The effects of changes in your body resulting from stopping smoking, with or without treatment with CHAMPIX, may alter the way other drugs work. Tell your doctor about all your other medicines, including prescription and nonprescription medicines, vitamins and herbal supplements. Especially, tell your doctor if you take:

- Insulin
- Asthma medicines (theophylline)
- Blood thinner (warfarin)

as an adjustment of the dose of these medicines may be necessary once you are smoke-free.

Psychiatric Symptoms
Quitting smoking can be associated with changes in mood and behavior, with or without taking medication to help quit. Some patients taking CHAMPIX may experience unusual feelings of agitation, depressed mood, hostility, aggression, changes in behavior or have impulsive or disturbing thoughts such as thoughts of self-harm or harm to others.

Stop taking CHAMPIX right away and tell your doctor if you experience these symptoms in a way that is not typical for you, or if you have thoughts of self-harm or harm to others. In a few cases, these symptoms have occurred after stopping CHAMPIX (see **SIDE EFFECTS AND WHAT TO DO ABOUT THEM**).

It is not known if these symptoms occur more often in people treated with CHAMPIX compared to those attempting to quit without any medication, or with other smoking cessation medications.

Pregnancy
Talk to your doctor if you are pregnant or planning to become pregnant.

You should not take CHAMPIX while you are pregnant. It is unknown if CHAMPIX will harm your unborn baby.

It is best to stop smoking before you get pregnant.

Breastfeeding
You should ask your doctor or pharmacist for advice before taking any medication, including CHAMPIX, if you are breastfeeding, as the medecine may pass into breast milk.

CHAMPIX is not recommended for use in children under 18 years of age.

Accidental Injury, including while Driving, Operating Machinery
Do not engage in potentially hazardous tasks, such as driving a car or operating dangerous machines, until you know how CHAMPIX may affect you. In some cases, people have reported sleepiness, dizziness, blackouts, seizures or difficulty concentrating while driving.

Seizures
Tell your doctor if you have experienced seizures or have epilepsy before you start CHAMPIX treatment. Some people have reported seizures while taking CHAMPIX, both with and without a history of seizures.

Heart or Stroke Events
New or worse heart or blood vessel (cardiovascular) problems have been reported in people taking CHAMPIX, primarily in those who already have cardiovascular problems. From the information available to date, it is not possible to determine whether CHAMPIX increases the risk of heart or stroke events.

Tell your doctor if you have any changes in cardiovascular symptoms during treatment with CHAMPIX. Get emergency medical help right away if you have symptoms of a heart attack, including any of the following:

- Chest discomfort (uncomfortable pressure, squeezing, fullness or pain) that lasts more than a few minutes, or that goes away and comes back
- Pain or discomfort in one or both arms, back, neck, jaw or stomach
- Shortness of breath, sweating, nausea, vomiting, or feeling lightheaded associated with chest discomfort

Get emergency medical help right away if you have symptoms of a stroke, including any of the following:

- Weakness - Sudden loss of strength or sudden numbness in the face, arm or leg even if temporary.
- Trouble speaking - Sudden difficulty speaking or understanding or sudden confusion, even if temporary.

- Vision problems - Sudden trouble with vision, even if temporary.
- Headache - Sudden severe and unusual headache.
- Dizziness - Sudden loss of balance, especially with any of the above signs.

INTERACTIONS WITH THIS MEDICATION

Drinking alcohol during treatment with CHAMPIX may increase the risk of psychiatric symptoms.

Use of CHAMPIX with other therapies for smoking-cessation:
The safety and benefits of taking CHAMPIX in combination with other medicines for stopping smoking have not been studied. Taking CHAMPIX in combination with other smoking-cessation therapies (eg, nicotine replacement therapy) is therefore not recommended. Using CHAMPIX in combination with nicotine replacement therapies (eg, patch gum or inhaler) is not likely to increase your chances of quitting smoking, and it may result in more side effects than with CHAMPIX alone.

PROPER USE OF THIS MEDICATION

You are more likely to stop smoking if you are motivated to stop. Your doctor and pharmacist can provide advice, support and sources of further information to help ensure your attempt to stop smoking is successful.

To increase the chances of success, CHAMPIX should be used in combination with supportive counselling as recommended by your doctor. CHAMPIX was used in combination with supportive counselling in the clinical trials. At any time, you can also call government-funded toll-free provincial Quit Lines, to speak to a knowledgeable and supportive specialist; these phone numbers are available on the Health Canada website, or by calling 1-800-CHAMPIX.

Always take CHAMPIX exactly as your doctor or healthcare professional has told you. You should check with your doctor or pharmacist if you are not sure.

REMEMBER: This medication has been prescribed specifically for you. Do not give it to anyone else.

Setting Your Quit Date

Starting treatment before your quit date lets CHAMPIX build up in your body. You can keep smoking until your quit date.

There are two ways to set your quit date when using CHAMPIX. Talk to your doctor or healthcare professional about which way is best for you:

- Set a quit date when you will stop smoking. Start taking CHAMPIX 8 -14 days (1 to 2 weeks) before your quit date.

Or

- Start taking CHAMPIX, then quit smoking between Day 8 and Day 35 after the start of your treatment (ie between Weeks 2 and 5).

Either way, you take CHAMPIX for 12 weeks.

Write down, and keep in a visible or convenient place (for example on the fridge or on the CHAMPIX pack), the date that you started CHAMPIX, your quit date, and the date to stop taking CHAMPIX.

Make sure that you try to stop smoking on your quit date. If you slip-up and smoke after that target date, keep trying. Some people need a few weeks on CHAMPIX for it to work best.

Dosing Options:

After the Week 1 Dosing Schedule (see below), there are two dosing options: the dose can remain at 0.5 mg twice a day or go up to 1.0 mg twice a day.

Based on the limited data available, the two doses do not appear different in terms of either quit rates, or rates of serious psychiatric side effects (your doctor can provide more information).

Discussion with your doctor is important in order to choose the dose that is best for you.

Regardless of which dose is prescribed, the first week on CHAMPIX is the same, and is described in the following table:

Week 1 Dosing Schedule:

Day	Dose
Day 1 – 3	Take one white CHAMPIX 0.5 mg tablet once a day.
Day 4 - 7	Take one white CHAMPIX 0.5 mg tablet twice a day, once in the morning and once in the evening, at about the same time each day.

Week 2 (day 8) to the end of treatment: There are two dosing options

Continue on 0.5 mg twice a day

Day	Dose
Day 8- end of treatment	**0.5 mg twice a day:** Continue to take one white CHAMPIX 0.5 mg pill in the morning, and one in the evening, at about the same time each day

Or

Start taking 1.0 mg twice a day

Day	Dose
Day 8- end of treatment	**1.0 mg twice a day:** Take one light blue CHAMPIX 1.0 mg pill in the morning, and one in the evening, at about the same time each day

The maximum dose of CHAMPIX is 1.0 mg twice a day.

If needed, the dose can be changed depending on how well you tolerate CHAMPIX and how effective your doctor and you consider it is in helping you quit smoking. Your doctor will help decide what dose is right for you.

CHAMPIX should be taken after eating and with a full glass of water

You should take CHAMPIX for 12 weeks.

If you have stopped smoking after 12 weeks of treatment, your doctor may recommend additional weeks of CHAMPIX treatment.

Your doctor or pharmacist may recommend to gradually lower the dose at the end of the treatment period rather than stopping abruptly.

Can I smoke while taking CHAMPIX?

You can keep smoking prior to your quit date.

Smoking after your quit date will reduce your chance of breaking your smoking addiction.

Some people have reported a change in the taste of cigarettes after starting CHAMPIX.

Overdose:
If you accidentally take more CHAMPIX than your doctor prescribed, you must seek medical advice or go to the nearest hospital emergency department immediately. Take your medication with you.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
Do not take a double dose to make up for a forgotten tablet. It is important that you take CHAMPIX regularly at the same time each day. If you forget to take a dose, take it as soon as you remember, as long as it is within a few hours of the missed dose. If it is longer than that since the missed dose, or if you do not remember whether you took a dose or not, then skip that dose, and wait to take the next dose at the correct time.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Whether you are taking medication to stop smoking or not, the following are symptoms you may feel: depressed, short-tempered, frustrated or angry, nervous, impatient; have difficulty concentrating. Your appetite may increase, and you may gain some weight.

Like all medicines, CHAMPIX can cause side effects, although not everybody gets them.

The common side effects are mostly mild to moderate and these usually occur in the first weeks of treatment.

Some of the most common side effects you should be aware of include:

- Nausea, vomiting

- Trouble sleeping,
- Headache
- Abnormal dreams (vivid, unusual, or increased dreaming; rarely may include nightmares)
- Sleepiness, tiredness, dizziness
- Constipation, diarrhea, gas

Tell your doctor immediately if you experience unusual feelings of agitation, aggression, depressed mood, hostility, hallucinations, changes in behavior or suicidal thoughts. Stop taking CHAMPIX if you experience these symptoms in a way that is not typical for you, or if you have thoughts of self-harm or harm to others. These symptoms have been reported in patients trying to stop smoking with or without CHAMPIX. When symptoms were reported, most were during CHAMPIX treatment, but some were following discontinuation of CHAMPIX therapy. It is not known if these symptoms are related to CHAMPIX (see **WARNINGS AND PRECAUTIONS**).

Some people have allergic reactions to CHAMPIX. Some of these allergic reactions can be life-threatening and include: swelling of the face, mouth (lips, gums, tongue), and throat can cause trouble breathing. If you have these symptoms, stop taking CHAMPIX and seek immediate emergency medical attention.

Some people can have serious skin reactions while taking CHAMPIX. These can include rash, swelling, redness, and peeling of the skin. Some of these reactions can become life-threatening. If you have a rash with peeling skin, or blistering of the mouth, around the eyes or genitals, stop taking CHAMPIX and seek immediate emergency medical attention.

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

Symptom / effect		**Talk with your doctor or pharmacist**		**Stop taking drug and seek immediate emergency medical attention**
		Only if severe	**In all cases**	
Rare	**Allergic reaction such as:** redness, itching or swelling of your skin, hives, burning, stinging, swelling of the neck area, or any difficulty with breathing, not present before using this medicine			**X**
Rare	**Serious skin reactions such as:** peeling of the skin, or rash combined with blisters around the mouth, eyes or genitals.			**X**
Rare See Warnings & Precautions	**Psychiatric Symptoms**		**X**	**X (if severe, or if involves potential for harm to self or others)**
Unknown See Warnings and Precautions	Heart attack (chest pain often associated with left shoulder or jaw pain, feeling of constriction around chest and sweating)			**X**

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

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency medical attention
		Only if severe	In all cases	
Unknown See Warnings and Precautions	Stroke (symptoms include weakness and/or loss of sensation of limbs or face, difficulty speaking, clumsiness, visual loss)			**X**
Unknown See Warnings and Precautions	**Seizures:** Loss of consciousness with uncontrollable shaking (convulsion)			**X**

This is not a complete list of side effects. For any unexpected effects while taking CHAMPIX, contact your doctor or pharmacist.

REPORTING SUSPECTED SIDE EFFECTS

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

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

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

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

HOW TO STORE IT

Store CHAMPIX at room temperature (15°C – 30°C).

Keep out of the reach of children.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
http://www.Pfizer.ca
or by contacting the sponsor, Pfizer Canada Inc., at:
1-800-463-6001

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