CHAMPIX™

(Varenicline) Tablets

1 NAME OF THE MEDICINAL PRODUCT

CHAMPIX

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 0.5 mg of varenicline (as tartrate).
Each film-coated tablet contains 1 mg of varenicline (as tartrate).

3 PHARMACEUTICAL FORM

Film-coated tablets

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

CHAMPIX is indicated as an aid to smoking cessation treatment.

4.2 Posology and method of administration

Usual Dosage for Adults

Smoking cessation therapies are more likely to succeed for patients who are motivated to stop smoking and who are provided additional advice and support. Patients should be provided with appropriate educational materials and counseling to support the quit attempt.

The patient should set a date to stop smoking. CHAMPIX dosing should start one week before this date. Alternatively, the patient can begin CHAMPIX dosing and then quit smoking between days 8 and 35 of treatment (see section **5.1 Pharmacodynamic properties** - *Flexibility in Setting a Quit Date*).

The recommended dose of CHAMPIX is 1 mg twice daily following a 1-week titration as follows:

Days 1 – 3:	0.5 mg once daily
Days 4 – 7:	0.5 mg twice daily
Day 8 – End of treatment:	1 mg twice daily

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 at 1 mg twice daily is recommended for the maintenance of abstinence (see section **5.1 Pharmacodynamic properties** - *Maintenance of Abstinence Study*).

A gradual approach to quitting smoking with CHAMPIX should be considered for patients who are not able or willing to quit abruptly. Patients should reduce smoking during the first 12 weeks of treatment and quit by the end of that treatment period. Patients should then continue taking CHAMPIX for an additional 12 weeks for a total of 24 weeks of treatment (see section **5.1 Pharmacodynamic properties** – *Gradual approach to quitting smoking*).

Patients who do not succeed in stopping smoking during 12 weeks of initial therapy, or who relapse after treatment, should be encouraged to make another attempt once factors contributing to the failed attempt have been identified and addressed (see section **5.1 Pharmacodynamic properties** - *Study in Subjects Re-treated with CHAMPIX*).

Patients who cannot tolerate adverse effects of CHAMPIX may have the dose lowered temporarily or permanently.

CHAMPIX tablets should be swallowed whole with water. CHAMPIX can be taken with or without food.

Patients with renal insufficiency:

No dosage adjustment is necessary for patients with mild to moderate renal impairment. For patients with severe renal impairment, dosing should begin at 0.5 mg once daily for the first 3 days then increased to 1 mg once daily. There is insufficient clinical experience with varenicline in patients with end stage renal disease (see section **5.2 Pharmacokinetic properties** – *Patients with renal insufficiency*).

Patients with hepatic impairment:

No dosage adjustment is necessary for patients with hepatic impairment (see section **5.2 Pharmacokinetic properties** – *Patients with hepatic impairment*).

Use in elderly patients:

No dosage adjustment is necessary for elderly patients. Because elderly patients are more likely to have decreased renal function, prescribers should consider the renal status of an elderly patient (see above *Patients with renal insufficiency* and *section* **5.2 Pharmacokinetic properties** – *Patients with renal insufficiency* and *Use in elderly patients*).

Use in pediatric patients:

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.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

Warnings

Neuropsychiatric Symptoms and Suicidality

Serious neuropsychiatric symptoms have been reported in patients being treated with CHAMPIX. These post-marketing reports have included changes in mood (including depression and mania), psychosis, hallucinations, paranoia, delusions, homicidal ideation, hostility, agitation, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed suicide.

Some reported cases may have been complicated by the symptoms of nicotine withdrawal in patients who stopped smoking. Depressed mood may be a symptom of nicotine withdrawal. Depression, rarely including suicidal ideation, has been reported in smokers undergoing a smoking cessation attempt without medication. However, some of these symptoms have occurred in patients taking CHAMPIX who continued to smoke. When symptoms were reported, most were during CHAMPIX treatment, but some were following discontinuation of CHAMPIX therapy.

These events have occurred in patients with and without pre-existing psychiatric disease; some patients have experienced worsening of their psychiatric illnesses. All patients being treated with CHAMPIX should be observed for neuropsychiatric symptoms or worsening of pre-existing psychiatric illness.

A large randomized, double-blind, active and placebo-controlled study was conducted to compare the risk of serious neuropsychiatric events in patients with and without a history of psychiatric disorder treated for smoking cessation with CHAMPIX, bupropion, nicotine replacement therapy patch (NRT) or placebo. The primary safety endpoint was a composite of neuropsychiatric adverse events that have been reported in post-marketing experience. The use of CHAMPIX in patients with or without a history of psychiatric disorder was not associated with an increased risk of serious neuropsychiatric adverse events in the composite primary endpoint compared with placebo (see section **5.1 Pharmacodynamic properties** – *Study in Subjects with and without a History of Psychiatric Disorder*).

A causal relationship between serious neuropsychiatric events and CHAMPIX has not been established. Clinicians should advise patients and caregivers that the patient should stop taking CHAMPIX and contact a health care provider immediately if agitation, depressed mood, changes in behavior or thinking that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behavior. In many post-marketing cases, resolution of symptoms after discontinuation of CHAMPIX was reported, although in some cases the symptoms persisted, therefore, ongoing monitoring and supportive care should be provided until symptoms resolve.

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

Somnambulism

Cases of somnambulism have been reported in patients taking CHAMPIX. Some cases described harmful behavior to self, others, or property. Instruct patients to discontinue CHAMPIX and notify their healthcare provider if they experience somnambulism (see section **4.8 Undesirable effects).**

Angioedema and Hypersensitivity Reactions

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

Serious Skin Reactions

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

Cardiovascular Events

In a placebo-controlled clinical trial of CHAMPIX administered to patients with stable cardiovascular disease, with approximately 350 patients per treatment arm, but certain non-fatal cardiovascular events occurred more frequently in patients treated with CHAMPIX than in patients treated with placebo (see section **4.8 Undesirable effects**). No causal relationship between these events and CHAMPIX has been established. In a large smoking cessation trial that assessed CV safety in patients with and without a history of psychiatric disorder, major CV events (CV death, non-fatal MI, non-fatal stroke) were reported less frequently in patients treated with CHAMPIX compared to placebo. In these studies, major CV events were infrequent overall and all-cause and CV mortality was lower in patients treated with CHAMPIX compared to patients treated with placebo. Smoking is an independent and major risk factor for CV disease.

Table 1 below shows the incidence of deaths and of selected non-fatal serious cardiovascular events occurring more frequently in the CHAMPIX arm compared to the placebo arm. These events were adjudicated by an independent blinded committee. Non-fatal serious cardiovascular events not listed occurred at the same incidence or more commonly in the placebo arm. Patients

with more than one cardiovascular event of the same type are counted only once per row. Some of the patients requiring coronary revascularization underwent the procedure as part of management of non-fatal MI and hospitalization for angina.

Table 1. Mortality and Adjudicated Non-fatal Serious Cardiovascular Events in the Placebo-controlled CHAMPIX Trial in Patients with Stable Cardiovascular Disease

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

A meta-analysis of 15 clinical trials of ≥12 weeks treatment duration, including 7,002 patients (4,190 CHAMPIX, 2,812 placebo), was conducted to systematically assess the cardiovascular safety of CHAMPIX. The study in patients with stable cardiovascular disease described above was included in the meta-analysis. There were lower rates of all-cause mortality (CHAMPIX [0.14%]; placebo [0.25%]) and cardiovascular mortality (CHAMPIX [0.05%]; placebo [0.07%]) in the CHAMPIX arms compared with the placebo arms in the meta-analysis.

The key cardiovascular safety analysis included occurrence and timing of a composite endpoint of Major Adverse Cardiovascular Events (MACE), defined as cardiovascular death, non-fatal MI, and non-fatal stroke. These events included in the endpoint were adjudicated by a blinded, independent committee. Overall, a small number of MACE occurred in the trials included in the meta-analysis, as described in Table 2. These events occurred primarily in patients with known cardiovascular disease.

Table 2. Number of MACE cases, Hazard Ratio and Rate Difference in a Meta-analysis of 15 Clinical Trials Comparing CHAMPIX to Placebo*

	CHAMPIX N = 4,190	Placebo N = 2,812
MACE cases, n (%)	13 (0.31%)	6 (0.21%)
Patient-years of exposure	1,316	839
Hazard ratio (95% CI)		
	1.95 (0.79, 4.82)	

Rate difference per 1,000 patient-years (95% CI)		
	6.30 (-2.40, 15.10)	

*Includes MACE occurring up to 30 days post-treatment.

The meta-analysis showed that exposure to CHAMPIX resulted in a hazard ratio for MACE of 1.95 (95% confidence interval from 0.79 to 4.82) for patients up to 30 days after treatment; this is equivalent to an estimated increase of 6.3 MACE events per 1,000 patient-years of exposure. The meta-analysis showed higher rates of CV endpoints in patients on CHAMPIX relative to placebo across different time frames and pre-specified sensitivity analyses, including various study groupings and CV outcomes. Although these findings were not statistically significant, they were consistent. Because the number of events was small overall, the power for finding a statistically significant difference in a signal of this magnitude is low.

CHAMPIX was not studied in patients with unstable cardiovascular disease or cardiovascular events occurring within two months before screening. Patients should be advised to notify a health care provider of new or worsening symptoms of cardiovascular disease. The risks of 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.

Precautions

General

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 mg twice daily after an initial week of dose titration. In patients taking CHAMPIX 0.5 mg twice daily, the incidence of nausea was 16% following initial titration. Approximately 3% of subjects treated with CHAMPIX 1 mg twice daily in studies involving 12 weeks of treatment discontinued treatment prematurely because of nausea. For patients with intolerable nausea, dose reduction should be considered.

Accidental Injury

There have been post-marketing reports of traffic accidents, near-miss incidents in traffic, or other accidental injuries in patients taking CHAMPIX. In some cases, the patients reported somnolence, dizziness, loss of consciousness or difficulty concentrating that resulted in impairment, or concern about potential impairment, in driving or operating machinery. Patients should be advised not to drive or operate machinery or engage in other potentially hazardous activities until they know how CHAMPIX may affect them.

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) (see section **4.5 Interaction with other medicinal products and other forms of interaction** – *Warfarin*).

At the end of treatment, discontinuation of CHAMPIX was associated with an increase in irritability, urge to smoke, depression, and/or insomnia in up to 3% of patients.

Seizures

In clinical trials and post-marketing experience, there have been reports of seizures in patients with or without a history of seizures, treated with CHAMPIX. CHAMPIX should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold. Causal relationship between these reports and CHAMPIX use has not been established.

4.5 Interaction with other medicinal products and other forms of interaction

Based on varenicline characteristics and clinical experience to date, CHAMPIX has no clinically meaningful pharmacokinetic drug interactions. No dosage adjustment of CHAMPIX or co-administered drugs listed below is recommended.

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

In vitro studies demonstrated that varenicline does not inhibit human renal transport proteins at therapeutic concentrations. Therefore, drugs that are cleared by renal secretion (e.g. 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, OCT2. Co-administration with inhibitors of OCT2 may not require a dose adjustment of CHAMPIX as the increase in systemic exposure to CHAMPIX is not expected to be clinically meaningful (see ***Cimetidine*** interaction below). 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 section **5.2 Pharmacokinetic properties** – *Metabolism*) and therefore a dose adjustment of CHAMPIX would not be required.

Metformin: When co-administered to 30 smokers varenicline (1 mg twice daily) did not alter the steady-state pharmacokinetics of metformin (500 mg twice daily), which is a substrate of OCT2. Metformin had no effect on varenicline steady-state pharmacokinetics.

Cimetidine: Co-administration of an OCT2 inhibitor, cimetidine (300 mg four times daily), with varenicline (2 mg single dose) 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.

Digoxin: Varenicline (1 mg twice daily) did not alter the steady-state pharmacokinetics of digoxin administered as a 0.25 mg daily dose in 18 smokers.

Warfarin: Varenicline (1 mg twice daily) 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 varenicline. Smoking cessation itself may result in changes to warfarin pharmacokinetics (see section **4.4 Special warnings and precautions for use** – *Effect of smoking cessation*).

Alcohol: There are limited clinical data on any potential interaction between alcohol and CHAMPIX. There have been post-marketing reports of increased intoxicating effects of alcohol in patients treated with varenicline. A causal relationship between these events and varenicline use has not been established.

Use with other therapies for smoking cessation:

Bupropion: Varenicline (1 mg twice daily) did not alter the steady-state pharmacokinetics of bupropion (150 mg twice daily) in 46 smokers. The safety of the combination of bupropion and varenicline has not been established.

Nicotine replacement therapy (NRT): Although co-administration of varenicline (1 mg twice daily) and transdermal nicotine (21 mg/day) for up to 12 days did not affect nicotine pharmacokinetics, the incidence of nausea, headache, vomiting, dizziness, dyspepsia and fatigue was greater for the combination than for NRT alone. 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, eight of twenty-two (36%) subjects treated with the combination of varenicline and NRT prematurely discontinued treatment due to adverse events, compared to 1 of 17 (6%) of subjects treated with NRT and placebo.

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

4.6 Pregnancy and lactation

Pregnancy:

A moderate amount of data on pregnant women (between 300-1000 pregnancy outcomes) indicated no malformative or fetal/neonatal toxicity of CHAMPIX (see section **5.1 Pharmacodynamic properties**).

Animal studies have shown reproductive toxicity (see section **5.3 Preclinical safety data**). As a precautionary measure, it is preferable to avoid the use of CHAMPIX during pregnancy (see section **5.1 Pharmacodynamic properties**).

Lactation:

Although it is not known whether this drug is excreted in human milk, animal studies have demonstrated that varenicline can be transferred to nursing pups. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from CHAMPIX, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Labour and delivery:

The potential effects of CHAMPIX on labor and delivery are not known.

4.7 Effects on ability to drive and use machines

Patients should be advised to use caution driving or operating machinery until they know how quitting smoking and/or varenicline may affect them.

4.8 Undesirable effects

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. Smoking cessation, with or without pharmacotherapy, has also been associated with the exacerbation of underlying psychiatric illness. No attempt has been made in either the design or the analysis of the CHAMPIX studies to distinguish between adverse events associated with study drug treatment or those possibly associated with nicotine withdrawal.

Pre-marketing development clinical trials included approximately 4,000 patients treated with CHAMPIX for up to 1 year (average exposure 84 days). In general, when adverse reactions occurred, onset was in the first week of therapy; severity was generally mild to moderate and there were no differences by age, race or gender with regard to the incidence of adverse reactions.

In patients treated with the recommended dose of 1 mg twice daily following an initial titration period, the adverse event most commonly reported was nausea (28.6%). In the majority of cases nausea occurred early in the treatment period, was mild to moderate in severity and seldom resulted in discontinuation.

The treatment discontinuation rate due to adverse events was 11.4% for CHAMPIX compared with 9.7% for placebo. In this group, the discontinuation rates for the most common adverse events in CHAMPIX treated patients were as follows: nausea (2.7% vs. 0.6% for placebo), headache (0.6% vs. 1.0% for placebo), insomnia (1.3% vs. 1.2% for placebo), and abnormal dreams (0.2% vs. 0.2% for placebo).

All adverse drug reactions (ADRs) listed in the table below are presented by the Medical Dictionary for Regulatory Activities (MedDRA, Version 16) System Organ Class (SOC), based on evaluation of data from pre-marketing phase 2-3 studies and updated based on pooled data from 18 placebo-controlled pre- and post-marketing studies, including approximately 5,000 patients treated with CHAMPIX. Within each category, the ADRs are presented in order of frequency, and then by decreasing order of clinical importance.

Adverse Reaction Table

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Rare ≥1/10,000 to <1/1,000
Infections and infestations	Nasopharyngitis	Bronchitis; Sinusitis		
Blood and lymphatic system disorders				Platelet count decreased
Metabolism and nutritional disorders		Weight increased; Decreased appetite; Increased appetite		Polydipsia
Psychiatric disorders	Abnormal dreams[a]; Insomnia[b]		Thinking abnormal; Restlessness; Mood swings; Libido decreased	Dysphoria; Bradyphrenia
Nervous system disorders	Headache	Somnolence; Dizziness; Dysgeusia	Tremor; Lethargy; Hypoaesthesia	Dysarthria; Coordination abnormal; Hypogeusia; Circadian rhythm sleep disorder
Eye disorders			Conjunctivitis; Eye pain	Scotoma; Photophobia
Ear and labyrinth disorders			Tinnitus	
Cardiac disorders			Angina pectoris; Tachycardia; Palpitations; Heart rate increased	Atrial fibrillation; Electrocardiogram ST segment depression; Electrocardiogram T wave amplitude decreased
Vascular disorders			Blood pressure increased; Hot flush	
Respiratory,		Dyspnoea;	Upper respiratory	Snoring

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Rare ≥1/10,000 to <1/1,000
thoracic and mediastinal disorders		Cough	tract inflammation; Respiratory tract congestion; Dysphonia; Rhinitis allergic; Throat irritation; Sinus congestion; Upper-airway cough syndrome; Rhinorrhoea	
Gastrointestinal disorders	Nausea	Gastrooesophageal reflux disease; Vomiting; Constipation; Diarrhoea; Abdominal distension; Abdominal pain[c]; Toothache; Dyspepsia; Flatulence; Dry mouth	Haematochezia; Gastritis; Eructation; Aphthous stomatitis; Gingival pain	Haematemesis
Skin and subcutaneous tissue disorders		Rash; Pruritus[d]	Erythema; Acne; Hyperhidrosis	
Musculoskeletal and connective tissue disorders		Arthralgia; Myalgia; Back pain	Muscle spasms	Joint stiffness
Renal and urinary disorders			Pollakiuria; Nocturia	Glycosuria; Polyuria
Reproductive system and breast disorders			Menorrhagia	Sexual dysfunction
General disorders and administration site conditions		Chest pain; Fatigue	Chest discomfort; Influenza like illness; Pyrexia; Asthenia; Malaise	
Investigations		Liver function test abnormal		

[a] Includes PTs Abnormal dreams and Nightmare.
[b] Includes PTs Insomnia, Initial insomnia, Middle insomnia and Terminal insomnia.
[c] Includes PTs Abdominal pain, Gastrointestinal pain Abdominal tenderness, Abdominal pain lower, Abdominal pain upper and Abdominal discomfort.
[d] Includes PTs Pruritus and Pruritus generalized.

ADRs frequencies are based on treatment-emergent all causality adverse events from 18 placebo-controlled smoking cessation studies (A3051002, A3051007, A3051016, A3051028, A3051036, A3051037, A3051045, A3051046_48, A3051049, A3051054, A3051055, A3051072, A3051080, A3051095, A3051104, A3051115, A3051122 and A3051139).

CIOMS III categories: Very Common ≥1/10 (≥10%); Common ≥1/100 to <1/10 (≥1% and <10%); Uncommon ≥1/1,000 to <1/100 (≥0.1% and <1%); Rare ≥1/10,000 to <1/1,000 (≥0.01% and <0.1%); Very Rare <1/10,000 (<0.01%).

CHAMPIX has also been studied in a trial conducted in patients with stable cardiovascular disease, a trial conducted in patients with chronic obstructive pulmonary disease (COPD) and a trial conducted in generally healthy patients (similar to those in the pre-marketing studies) in which they were allowed to select a quit date between Days 8 and 35 of treatment ("alternative quit date instruction trial").

In the trial of patients with stable cardiovascular disease, more types and a greater number of cardiovascular events were reported compared to pre-marketing studies. Treatment-emergent (on-treatment or 30 days after treatment) cardiovascular events reported with a frequency ≥1% in either treatment group in this study were angina pectoris (3.7% and 2.0% for varenicline and placebo, respectively), chest pain (2.5% vs. 2.3%), peripheral edema (2.0% vs. 1.1%), hypertension (1.4% vs. 2.6%), and palpitations (0.6% vs. 1.1%). Deaths and serious cardiovascular events occurring over the 52 weeks of the study (treatment-emergent and non-treatment-emergent) were adjudicated by a blinded, independent committee. The following treatment-emergent adjudicated events occurred with a frequency ≥1% in either treatment group: non-fatal MI (1.1% vs. 0.3% for varenicline and placebo, respectively), and hospitalization for angina pectoris (0.6% vs. 1.1%). During non-treatment follow up to 52 weeks, the adjudicated events included need for coronary revascularization (2.0% vs. 0.6%), hospitalization for angina pectoris (1.7% vs. 1.1%), and new diagnosis of peripheral vascular disease (PVD) or admission for a PVD procedure (1.4% vs. 0.6%). Some of the patients requiring coronary revascularization underwent the procedure as part of management of non-fatal MI and hospitalization for angina. Cardiovascular death occurred in 0.3% of patients in the varenicline arm and 0.6% of patients in the placebo arm over the course of the 52-week study.

Adverse events in the trial of patients with COPD and in the alternative quit date instruction trial were quantitatively and qualitatively similar to those observed in pre-marketing studies.

There have been reports of somnambulism, some resulting in harmful behavior to self, others, or property in patients treated with CHAMPIX (see section **4.4 Special warnings and precautions for use**).

4.8.1 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 possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

There have been reports of depression, mania, psychosis, hallucinations, paranoia, delusions, homicidal ideation, aggression, hostility, anxiety, and panic, as well as suicidal ideation, suicide attempt and completed suicide in patients attempting to quit smoking while taking CHAMPIX (see section **4.4 Special warnings and precautions for use**). Smoking cessation with or without treatment is associated with nicotine withdrawal symptoms and the exacerbation of underlying psychiatric illness. Not all patients had known pre-existing psychiatric illness and not all had discontinued smoking. The role of CHAMPIX in these reports is not known.

There have been reports of hypersensitivity reactions, including angioedema (see section **4.4 Special warnings and precautions for use**).

There have also been reports of serious skin reactions, including Stevens-Johnson syndrome and Erythema Multiforme in patients taking CHAMPIX (see section **4.4 Special warnings and precautions for use**).

4.9 Overdose

No cases of overdose were reported in pre-marketing clinical trials.

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

Varenicline has been shown to be dialyzed in patients with end-stage renal disease (see section **5.2 Pharmacokinetic properties** – *Patients with renal insufficiency*), however, there is no experience in dialysis following overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Varenicline binds with high affinity and selectivity at α4β2 neuronal nicotinic acetylcholine receptors, where it acts as a partial agonist - a compound that has both agonist activity, with lower intrinsic efficacy than nicotine, and antagonist activities in the presence of nicotine. The efficacy of CHAMPIX in smoking cessation is believed to be the result of varenicline's activity at a sub-type of the nicotinic receptor where its binding produces agonist activity, while simultaneously preventing nicotine binding to α4β2 receptors.

Electrophysiology studies *in vitro* and neurochemical studies *in vivo* have shown that varenicline binds to $\alpha_4\beta_2$ neuronal nicotinic acetylcholine receptors and stimulates receptor-mediated activity, but at a significantly lower level than nicotine. Nicotine competes for the same human α4β2 nAChR binding site for which CHAMPIX has higher affinity. Varenicline blocks the ability of nicotine to activate α4β2 receptors and thus to stimulate the central nervous mesolimbic dopamine system, believed to be the neuronal mechanism underlying reinforcement and reward experienced upon smoking. Varenicline is highly selective and binds more potently to α4β2 receptors (Ki = 0.15 nM) than to other common nicotinic receptors (>500-fold $\alpha_3\beta_4$ (Ki = 84 nM), >3500-fold α_7 (Ki = 620 nM), >20,000-fold α1βγδ (Ki = 3,400 nM)), or to non-nicotinic receptors and transporters (>2000-fold (Ki > 1μM)). Varenicline also binds with moderate affinity (Ki = 350 nM) to the 5-HT3 receptor.

Clinical Efficacy and Safety:

The efficacy of CHAMPIX in smoking cessation was demonstrated in 3 pre-marketing clinical trials involving chronic cigarette smokers (≥10 cigarettes per day). 2619 patients received varenicline 1 mg twice daily (titrated during the first week), 669 patients received bupropion 150 mg twice daily (also titrated) and 684 patients received placebo.

Comparative Clinical Studies:

Two identically designed double-blind clinical trials prospectively compared the efficacy of CHAMPIX (1 mg twice daily), sustained release bupropion (150 mg twice daily) and placebo in smoking cessation. In these 52-week duration studies, patients received treatment for 12 weeks, followed by a 40-week non-treatment phase.

In all studies, patients were provided with an educational booklet on smoking cessation and received up to 10 minutes of smoking cessation counseling at each weekly treatment visit according to Agency for Healthcare Research and Quality guidelines. Patients set a date to stop smoking (target quit date, TQD) with dosing starting 1 week before this date.

The primary endpoint of the two studies was the carbon monoxide (CO) confirmed, 4-week continuous quit rate (4W-CQR) from week 9 through week 12. The primary endpoint for CHAMPIX demonstrated statistical superiority to bupropion and placebo.

After the 40-week non-treatment phase, a key secondary endpoint for both studies was the Continuous Abstinence Rate (CA) at Week 52. CA was defined as the proportion of all subjects treated who did not smoke (not even a puff of a cigarette) from Week 9 through Week 52 and did not have an exhaled CO measurement of >10 ppm. The 4W-CQR (weeks 9 through 12) and CA rate (weeks 9 through 52) from studies 1 and 2 are included in the following table:

	Study 1 (n = 1022)		Study 2 (n = 1023)	
	4W CQR	CA Wk 9-52	4W CQR	CA Wk 9-52
CHAMPIX	44.4%	22.1%	44.0%	23.0%
Bupropion	29.5%	16.4%	30.0%	15.0%
Placebo	17.7%	8.4%	17.7%	10.3%
Odds ratio Varenicline vs. placebo	3.91 p <0.0001	3.13 p <0.0001	3.85 p <0.0001	2.66 p <0.0001
Odds ratio Varenicline vs. bupropion	1.96 p <0.0001	1.45 p = 0.0640	1.89 p <0.0001	1.72 P = 0.0062

Patient reported craving, withdrawal and reinforcing effects of smoking:

Across both Studies 1 and 2 during active treatment, Patient Reported Outcomes measures demonstrated that craving and withdrawal were significantly reduced in patients randomized to CHAMPIX in comparison with placebo. CHAMPIX also significantly reduced reinforcing effects of smoking that can perpetuate smoking behavior in patients who smoke during treatment compared with placebo. The effect of CHAMPIX on craving, withdrawal and reinforcing effects of smoking were not measured during the non-treatment long-term follow-up phase.

Maintenance of Abstinence Study:

The third study assessed the benefit of an additional 12 weeks of varenicline therapy on the maintenance of abstinence. Patients in this study (n = 1,927) received open-label varenicline 1 mg twice daily for 12 weeks. Patients who stopped smoking by Week 12 were then randomized to receive either varenicline (1 mg twice daily) or placebo for an additional 12 weeks for a total study duration of 52 weeks.

The primary study endpoint was the CO-confirmed continuous abstinence rate from week 13 through week 24 in the double-blind treatment phase. A key secondary endpoint was the continuous abstinence (CA) rate for week 13 through week 52.

This study showed the benefit of an additional 12-week treatment with varenicline 1 mg twice daily for the maintenance of smoking cessation compared to placebo. The odds of maintaining abstinence at week 24, following an additional 12 weeks of treatment with varenicline, were 2.47 times those for placebo ($p < 0.0001$). Superiority to placebo for CA was maintained through week 52 (Odds Ratio=1.35, $p = 0.0126$).

The key results are summarized in the following table:

	Varenicline n = 602	Placebo n = 604	Difference (95% CI)	Odds ratio (95% CI)
CA wk 13-24	70.6%	49.8%	20.8% (15.4%, 26.2%)	2.47 (1.95, 3.15)
CA wk 13-52	44.0%	37.1%	6.9% (1.4%,12.5%)	1.35 (1.07, 1.70)

Study in Subjects 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 twice daily (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.

Patients treated with CHAMPIX had a superior rate of CO-confirmed abstinence during weeks 9 through 12 (45.0%) compared to patients treated with placebo (11.8%) (odds ratio 7.08; 95% CI 4.34, 11.55; $p < 0.0001$) and from weeks 9 through 52 (20.1%) compared to subjects treated with placebo (3.3%) (odds ratio 9.00; 95% CI 3.97, 20.41; $p < 0.0001$).

Adverse events in this study were quantitatively and qualitatively similar to those observed in pre-marketing studies.

The key results are summarized in the following table:

	CHAMPIX n = 249	Placebo n = 245	Odds ratio (95% CI), p value
CA wk 9-12	45.0%	11.8%	7.08 (4.34, 11.55) p <0.0001
CA wk 9-52	20.1%	3.3%	9.00 (3.97, 20.41) p <0.0001

Gradual approach to quitting smoking:

CHAMPIX was evaluated in a 52-week double-blind placebo-controlled study of 1,510 subjects who were not able or willing to quit smoking within four weeks, but were willing to gradually reduce their smoking over a 12 week period before quitting. Subjects were randomized to either CHAMPIX 1 mg twice daily (n = 760) or placebo (n = 750) for 24 weeks and followed up post-treatment through week 52. Subjects were instructed to reduce the number of cigarettes smoked by at least 50% by the end of the first four weeks of treatment, followed by a further 50 percent reduction from week four to week eight of treatment, with the goal of reaching complete abstinence by 12 weeks. After the initial 12-week reduction phase, subjects continued treatment for another 12 weeks. Subjects treated with CHAMPIX had a significantly higher Continuous Abstinence Rate compared with placebo at weeks 15 through 24 (32.1% vs. 6.9%; odds ratio 8.74; 95% CI 6.09, 12.53; p<0.0001) and weeks 21 through 52 (27.0% vs. 9.9%; odds ratio 4.02; 95% CI 2.94, 5.50; p<0.0001).

The key results are summarized in the following table:

	Varenicline n = 760	Placebo n = 750	Odds ratio (95% CI), p value
CA wk 15-24	32.1%	6.9%	8.74 (6.09, 12.53) p<0.0001
CA wk 21-52	27.0%	9.9%	4.02 (2.94, 5.50) p<0.0001

The CHAMPIX safety profile in this study was consistent with the premarketing studies.

Study in Subjects with Cardiovascular Disease:

CHAMPIX was evaluated in a randomized, double-blind, placebo-controlled study of 703 subjects with stable, documented cardiovascular disease (other than or in addition to hypertension) that had been diagnosed for more than 2 months. Subjects aged 35 to 75 years were randomized to CHAMPIX 1 mg twice daily or placebo for a treatment of 12 weeks and then were followed for 40 weeks post-treatment. Subjects treated with CHAMPIX had a superior rate of CO-confirmed abstinence during weeks 9 through 12 (47.3%) compared to subjects treated with placebo (14.3%) (odds ratio 6.05; 95% CI 4.13, 8.86; $p < 0.0001$) and from week 9 through 52 (19.8%) compared to subjects treated with placebo (7.4%) (odds ratio 3.19; 95% CI 1.97, 5.18; $p <0.0001$). Deaths and serious cardiovascular events occurring over the 52 weeks of the study (treatment-emergent and non-treatment-emergent) were adjudicated by a blinded, independent committee. The following treatment-emergent adjudicated events occurred with a frequency ≥1% in either treatment group: non-fatal myocardial infarction (1.1% vs. 0.3% for varenicline and placebo, respectively), and hospitalization for angina pectoris (0.6% vs. 1.1%). During non-treatment follow up to 52 weeks, adjudicated events with a frequency ≥1% included need for coronary revascularization (2.0% vs. 0.6%), hospitalization for angina pectoris (1.7% vs. 1.1%), and new diagnosis of peripheral vascular disease (PVD) or admission for a PVD procedure (1.4% vs. 0.6%). Some of the patients requiring coronary revascularization underwent the procedure as part of management of non-fatal MI and hospitalization for angina. Cardiovascular death occurred in 0.3% of patients in the varenicline arm and 0.6% of patients in the placebo arm over the course of the 52 week study. (See section **4.4 Special warning and precautions for use**).

The key results are summarized in the following table:

	CHAMPIX n = 353	Placebo n = 350	Odds ratio (95% CI), p value
CA wk 9-12	47.3%	14.3%	6.05 (4.13, 8.86) p <0.0001
CA wk 9-52	19.8%	7.4%	3.19 (1.97, 5.18) p <0.0001

Cardiovascular Safety Assessment Study in Subjects with and without a History of Psychiatric Disorder:

The cardiovascular (CV) safety of CHAMPIX was evaluated in the Cardiovascular Safety Assessment Study in subjects with and without a history of psychiatric disorder (parent study) and in a non-treatment extension study. In the parent study (N = 8058), subjects aged 18-75 years, smoking 10 or more cigarettes per day were randomized 1:1:1:1 to CHAMPIX 1 mg BID, bupropion SR 150 mg BID, nicotine replacement therapy patch (NRT) 21 mg/day with taper or placebo for a treatment period of 12 weeks; they were then followed for another 12 weeks post-treatment. The non-treatment extension study enrolled 4595 of the 6293 subjects who completed the parent study and followed them through week 52. Of all treated subjects, 1749 (21.7%) had a medium CV risk and 644 (8.0%) had a high CV risk, as defined by Framingham score.

The primary CV endpoint was the time to major adverse cardiovascular event (MACE), defined as cardiovascular death, non-fatal myocardial infarction or non-fatal stroke during treatment. Deaths and cardiovascular events were adjudicated by a blinded, independent committee.

The following table shows the incidence of MACE and Hazard Ratios vs placebo for all treatment groups during treatment, and cumulative for treatment plus 30 days and through end of study.

	Varenicline N=2016	**Bupropion N=2006**	**NRT N=2022**	**Placebo N=2014**
During treatment				
MACE, n (%)	1 (0.05)	2 (0.10)	1 (0.05)	4 (0.20)
Hazard Ratio (95% CI) vs placebo	0.29 (0.05, 1.68)	0.50 (0.10, 2.50)	0.29 (0.05, 1.70)	
During treatment plus 30 days				
MACE, n (%)	1 (0.05)	2 (0.10)	2 (0.10)	4 (0.20)
Hazard Ratio (95% CI) vs placebo	0.29 (0.05, 1.70)	0.51 (0.10, 2.51)	0.50 (0.10, 2.48)	
Through end of study				
MACE, n (%)	3 (0.15)	9 (0.45)	6 (0.30)	8 (0.40)
Hazard Ratio (95% CI) vs placebo	0.39 (0.12, 1.27)	1.09 (0.42, 2.83)	0.75 (0.26, 2.13)	

Incidence of MACE + (defined as any MACE or a new onset or worsening peripheral vascular disease (PVD) requiring intervention, a need for coronary revascularization, or hospitalization for unstable angina) and all cause deaths are shown for all treatment groups during treatment, and cumulative for treatment plus 30 days and through end of study in the following table.

	Varenicline N=2016	**Bupropion N=2006**	**NRT N=2022**	**Placebo N=2014**
During treatment				
MACE+, n (%)	5 (0.25)	4 (0.20)	2 (0.10)	5 (0.25)
All cause deaths, n (%)	0	2 (0.10)	0	2 (0.10)
During treatment plus 30 days				
MACE+, n (%)	5 (0.25)	4 (0.20)	3 (0.15)	7 (0.35)
All cause deaths, n (%)	0	2 (0.10)	0	2 (0.10)
Through end of study				
MACE+, n (%)	10 (0.50)	15 (0.75)	10 (0.49)	12 (0.60)
All cause deaths, n (%)	2 (0.10)	4 (0.20)	3 (0.15)	4 (0.20)

The use of CHAMPIX, bupropion, and NRT was not associated with an increased risk of CV AEs in smokers treated for up to 12 weeks and followed for up to 1 year compared to placebo, although because of the relatively low number of events overall, an association cannot be entirely ruled out. The number of subjects with MACE, MACE + and all cause deaths was similar or lower for the CHAMPIX-treated subjects compared to those treated with placebo. (See section **4.4 Special warnings and precautions for use**).

Study in Subjects with Chronic Obstructive Pulmonary Disease:

CHAMPIX was evaluated in a randomized, double-blind, placebo-controlled study of 499 subjects with mild-to-moderate Chronic Obstructive Pulmonary Disease with post-bronchodilator FEV1/FVC <70% and FEV1 ≥50% of predicted normal value. Subjects aged ≥35 years were randomized to CHAMPIX 1 mg twice daily or placebo for a treatment of 12 weeks and then were followed for 40 weeks post-treatment. Subjects treated with CHAMPIX had a superior rate of CO-confirmed abstinence during weeks 9 through 12 (42.3%) compared to subjects treated with placebo (8.8%) (odds ratio 8.40; 95% CI 4.99, 14.14; p <0.0001) and from week 9 through 52 (18.6%) compared to subjects treated with placebo (5.6%) (odds ratio 4.04; 95% CI 2.13, 7.67; p <0.0001). Adverse events in this study were quantitatively and qualitatively similar to those observed in pre-marketing studies.

The key results are summarized in the following table:

	CHAMPIX n = 248	Placebo n = 251	Odds ratio (95% CI), p value
CA wk 9-12	42.3%	8.8%	8.40 (4.99, 14.14) p <0.0001
CA wk 9-52	18.6%	5.6%	4.04 (2.13, 7.67) p <0.0001

Study in Subjects 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 in the past 2 years and were successfully treated. Subjects aged 18 to 75 years were randomized to CHAMPIX 1 mg twice daily or placebo for a treatment of 12 weeks and then followed for 40 weeks post-treatment. Subjects treated with CHAMPIX had a superior rate of CO-confirmed abstinence during weeks 9 through 12 (35.9%) compared to subjects treated with placebo (15.6%) (odds ratio 3.35; 95% CI 2.16, 5.21; p <0.0001) and from week 9 through 52 (20.3%) compared to subjects treated with placebo (10.4%) (odds ratio 2.36; 95% CI 1.40, 3.98; p = 0.0011).

The most common adverse events (≥10%) in subjects taking CHAMPIX were nausea (27.0% vs. 10.4% on placebo), headache (16.8% vs. 11.2%) abnormal dreams (11.3% vs. 8.2%), insomnia (10.9% vs. 4.8%) and irritability (10.9% vs. 8.2%). Additionally, the following psychiatric AEs were reported in ≥2% of patients in either treatment group (CHAMPIX or placebo, respectively): anxiety (7.0% vs. 9.3%), agitation (6.6% vs. 4.1%), depression (6.6% vs. 4.8%), tension (3.5% vs. 3.0%), depressed mood (2.7% vs. 3.7%), sleep disorder (2.7% vs. 1.5%), hostility (2.0% vs.

0.4%) and restlessness (2.0% vs. 1.9%). Psychiatric scales showed no differences between the CHAMPIX and placebo groups and no overall worsening of depression during the study in either treatment group.

The percentage of subjects with suicidal ideation and/or behavior was similar between the CHAMPIX and placebo groups during treatment (6.0% and 7.5%, respectively) and the non- treatment follow-up (6.2% and 5.8%, respectively).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.

The key efficacy results are summarized in the following table:

	CHAMPIX n = 256	Placebo n = 269	Odds ratio (95% CI), p value
CA wk 9-12	35.9	15.6	3.35 (2.16, 5.21) p <0.0001
CA wk 9-52	20.3	10.4	2.36 (1.40, 3.98) p = 0.0011

Study in Subjects 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 CHAMPIX (1 mg twice daily) or placebo for 12 weeks with 12-week non-drug follow-up.

The most common adverse events in subjects taking CHAMPIX were nausea (23.8% vs. 14.0% on placebo), headache (10.7% vs. 18.6% on placebo) and vomiting (10.7% vs. 9.3% on placebo). Among reported neuropsychiatric adverse events, insomnia was the only event reported in either treatment group in ≥5% of subjects at a rate higher in the CHAMPIX group than in placebo (9.5% vs. 4.7%).

Overall, there was no worsening of schizophrenia in either treatment group as measured by psychiatric scales and there were no overall changes in extra-pyramidal signs.

In the CHAMPIX group compared to placebo, a higher proportion of subjects reported suicidal ideation or behavior prior to enrollment (lifetime history) and after the end of active treatment period (on Days 33 to 85 after the last dose of drugs). During the active treatment period, the incidence of suicide-related events was similar between the CHAMPIX-treated and the placebo-treated subjects (11% vs. 9.3%, respectively). The percentage of subjects with suicide-related events in the active treatment phase compared to post-treatment phase was unchanged in the CHAMPIX group; in the placebo group, this percentage was lower in the post-treatment phase. There were no completed suicides. There was one suicidal attempt in a CHAMPIX-treated subject whose lifetime history included several similar attempts. While these data do not suggest that CHAMPIX treatment causes or worsens suicidality in subjects with stable schizophrenia or schizoaffective disorder, the limited data available from this single smoking cessation study is not sufficient to allow definitive conclusions to be drawn.

Neuropsychiatric Safety Study in Subjects with and without a History of Psychiatric Disorder:

CHAMPIX was evaluated in a randomized, double-blind, active and placebo-controlled study that included subjects with a history of psychiatric disorder (psychiatric cohort, N = 4074) and subjects without a history of psychiatric disorder (non-psychiatric cohort, N = 3984). Subjects aged 18-75 years, smoking 10 or more cigarettes per day were randomized 1:1:1:1 to CHAMPIX 1 mg BID, bupropion SR 150 mg BID, nicotine replacement therapy patch (NRT) 21 mg/day with taper or placebo for a treatment period of 12 weeks; they were then followed for another 12 weeks post-treatment.

The primary safety endpoint was a composite of the following neuropsychiatric (NPS) adverse events: severe events of anxiety, depression, feeling abnormal, or hostility, and moderate or severe events of agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal ideation, suicidal behavior or completed suicide. (See section **4.4 Special warnings and precautions for use).**

The following table shows the rates of the composite NPS adverse event primary end point by treatment group and the risk differences (RDs) (95% CI) vs. placebo in the non-psychiatric cohort. The individual components of the endpoint are also shown. In addition, the table shows the subset of the endpoint comprised of only events of severe intensity:

	Non-psychiatric Cohort N=3984			
	CHAMPIX	**Bupropion**	**NRT**	**Placebo**
Number of Patients Treated	990	989	1006	999
Composite NPS AE Primary Endpoint, n (%)	13 (1.3)	22 (2.2)	25 (2.5)	24 (2.4)
RD (95% CI) vs. Placebo	-1.28 (-2.40, -0.15)	-0.08 (-1.37, 1.21)	-0.21 (-1.54,1.12)	
NPS AE Primary Endpoint Components n (%):				
Anxiety[a]	0	1 (0.1)	0	3 (0.3)
Depression[a]	1 (0.1)	0	0	0
Feeling abnormal[a]	0	0	0	0
Hostility[a]	0	1 (0.1)	1 (0.1)	0
Agitation[b]	10 (1.0)	11 (1.1)	19 (1.9)	11 (1.1)
Aggression[b]	3 (0.3)	3 (0.3)	2 (0.2)	3 (0.3)
Delusions[b]	0	0	1 (0.1)	0
Hallucinations[b]	1 (0.1)	0	0	0
Homicidal ideation[b]	0	0	1 (0.1)	0
Mania[b]	0	1 (0.1)	2 (0.2)	2 (0.2)
Panic[b]	0	4 (0.4)	1 (0.1)	3 (0.3)
Paranoia[b]	0	1 (0.1)	0	0
Psychosis[b]	0	0	1 (0.1)	0
Suicidal behavior[b]	0	1 (0.1)	1 (0.1)	0
Suicidal ideation[b]	0	1 (0.1)	2 (0.2)	3 (0.3)
Completed suicide[b]	0	0	0	1 (0.1)
Composite NPS AE Endpoint of				

severe intensity n (%)	1 (0.1)	4 (0.4)	3 (0.3)	5 (0.5)
NPS AE Endpoint Components of severe intensity n (%):				
Anxiety	0	1 (0.1)	0	3 (0.3)
Depression	1 (0.1)	0	0	0
Feeling abnormal	0	0	0	0
Hostility	0	1 (0.1)	1 (0.1)	0
Agitation	0	0	2 (0.2)	0
Aggression	1 (0.1)	1 (0.1)	0	0
Delusions	0	0	0	0
Hallucinations	0	0	0	0
Homicidal ideation	0	0	0	0
Mania	0	0	0	0
Panic	0	1 (0.1)	1 (0.1)	1 (0.1)
Paranoia	0	0	0	0
Psychosis	0	0	0	0
Suicidal behavior	0	1 (0.1)	0	0
Suicidal ideation	0	0	0	1 (0.1)
Completed suicide	0	0	0	1 (0.1)

AE=adverse event; [a]Grade=severe intensity AE; [b]Grade=moderate and severe intensity AE; NRT=Nicotine replacement therapy patch

In the non-psychiatric cohort, the rates of events in the composite endpoint were low across all treatment groups and were similar or lower for each of the active treatments compared to placebo: risk differences (RDs (95% Confidence Interval [CI])) vs. placebo were -1.28% (-2.40, -0.15) for CHAMPIX, -0.08% (-1.37, 1.21) for bupropion and -0.21% (-1.54, 1.12) for NRT. The use of CHAMPIX, bupropion and NRT in the non-psychiatric cohort was not associated with an increased risk of NPS adverse events in the composite primary endpoint compared with placebo (95% CIs were lower than or included zero). Similarly, the use of varenicline was not associated with an increased risk of NPS adverse events in the composite primary endpoint compared with bupropion or NRT in the non-psychiatric cohort (-1.19% (-2.30, -0.09) and -1.07 (-2.21, 0.08), respectively).

In non-psychiatric cohort, the percentage of subjects with suicidal ideation and/or behavior based on the Columbia-Suicide Severity Rating Scale (C-SSRS) was similar between the varenicline and placebo groups during treatment and in the non-treatment follow-up, as shown in the following table:

	Non-psychiatric Cohort N=3984			
	CHAMPIX N = 990 n (%)	**Bupropion N = 989 n (%)**	**NRT N = 1006 n (%)**	**Placebo N = 999 n (%)**
During treatment				
Number assessed	988	983	996	995
Suicidal behavior and/or ideation	7 (0.7)	4 (0.4)	3 (0.3)	7 (0.7)
Suicidal behavior	0	0	1 (0.1)	1 (0.1)
Suicidal ideation	7 (0.7)	4 (0.4)	3 (0.3)	6 (0.6)

During follow up				
Number assessed	807	816	800	805
Suicidal behavior and/or ideation	3 (0.4)	2 (0.2)	3 (0.4)	4 (0.5)
Suicidal behavior	0	1 (0.1)	0	0
Suicidal ideation	3 (0.4)	2 (0.2)	3 (0.4)	4 (0.5)

There was one completed suicide, which occurred during treatment in a subject treated with placebo in the non-psychiatric cohort.

The following table shows the rates of the composite NPS adverse event primary end point by treatment group and the risk differences (RDs) (95% CI) vs. placebo in the psychiatric cohort. The individual components of the endpoint are also shown. In addition, the table shows the subset of the endpoint comprised of only events of severe intensity:

	Psychiatric Cohort N=4074			
	CHAMPIX	**Bupropion**	**NRT**	**Placebo**
Number of Patients Treated	1026	1017	1016	1015
Composite NPS AE Primary Endpoint, n (%)	67 (6.5)	68 (6.7)	53 (5.2)	50 (4.9)
RD (95% CI) vs. Placebo	1.59 (-0.42, 3.59)	1.78 (-0.24, 3.81)	0.37 (-1.53, 2.26)	
NPS AE Primary Endpoint Components n (%):				
Anxiety[a]	5 (0.5)	4 (0.4)	6 (0.6)	2 (0.2)
Depression[a]	6 (0.6)	4 (0.4)	7 (0.7)	6 (0.6)
Feeling abnormal[a]	0	1 (0.1)	0	0
Hostility[a]	0	0	0	0
Agitation[b]	25 (2.4)	29 (2.9)	21 (2.1)	22 (2.2)
Aggression[b]	14 (1.4)	9 (0.9)	7 (0.7)	8 (0.8)
Delusions[b]	1 (0.1)	1 (0.1)	1 (0.1)	0
Hallucinations[b]	5 (0.5)	4 (0.4)	2 (0.2)	2 (0.2)
Homicidal ideation[b]	0	0	0	0
Mania[b]	7 (0.7)	9 (0.9)	3 (0.3)	6 (0.6)
Panic[b]	7 (0.7)	16 (1.6)	13 (1.3)	7 (0.7)
Paranoia[b]	1 (0.1)	0	0	2 (0.2)
Psychosis[b]	4 (0.4)	2 (0.2)	3 (0.3)	1 (0.1)
Suicidal behavior[b]	1 (0.1)	1 (0.1)	0	1 (0.1)
Suicidal ideation[b]	5 (0.5)	2 (0.2)	3 (0.3)	2 (0.2)
Completed suicide[b]	0	0	0	0
Composite NPS AE Endpoint of severe intensity n (%)	14 (1.4)	14 (1.4)	14 (1.4)	13 (1.3)
NPS AE Endpoint Components of severe intensity n (%):				
Anxiety	5 (0.5)	4 (0.4)	6 (0.6)	2 (0.2)
Depression	6 (0.6)	4 (0.4)	7 (0.7)	6 (0.6)
Feeling abnormal	0	1 (0.1)	0	0
Hostility	0	0	0	0
Agitation	1 (0.1)	1 (0.1)	4 (0.4)	2 (0.2)
Aggression	1 (0.1)	1 (0.1)	0	1 (0.1)
Delusions	0	0	0	0

Hallucinations	0	1 (0.1)	0	0
Homicidal ideation	0	0	0	0
Mania	2 (0.2)	1 (0.1)	0	0
Panic	0	1 (0.1)	0	1 (0.1)
Paranoia	0	0	0	0
Psychosis	0	1 (0.1)	1 (0.1)	0
Suicidal behavior	1 (0.1)	1 (0.1)	0	1 (0.1)
Suicidal ideation	1 (0.1)	0	1 (0.1)	0
Completed suicide	0	0	0	0

AE=adverse event; [a] Grade=severe intensity AE; [b] Grade=moderate and severe intensity AE; NRT=Nicotine replacement therapy patch

There were more events reported in patients in the psychiatric cohort in each treatment group compared with the non-psychiatric cohort. In the psychiatric cohort, the incidence of events in the composite endpoint was higher for each of the active treatments compared to placebo: RDs (95%CI) vs placebo were 1.59% (-0.42, 3.59) for CHAMPIX, 1.78% (-0.24, 3.81) for bupropion and 0.37% (-1.53, 2.26) for NRT. The use of CHAMPIX, bupropion and NRT in the psychiatric cohort was not associated with an increased risk of NPS adverse events in the composite primary endpoint compared with placebo (95% CIs included zero). Similarly, the use of CHAMPIX was not associated with an increased risk of NPS adverse events in the composite primary endpoint compared with bupropion or NRT in the psychiatric cohort (-0.20% (-2.34, 1.95) and 1.22% (-0.81, 3.25), respectively).

In the psychiatric cohort, the percentage of subjects with suicidal ideation and/or behavior based on the Columbia-Suicide Severity Rating Scale (C-SSRS) was similar between the CHAMPIX and placebo groups during treatment and in the non- treatment follow-up, as shown in the following table:

	Psychiatric Cohort N=4074			
	CHAMPIX N = 1026 n (%)	**Bupropion N = 1017 n (%)**	**NRT N = 1016 n (%)**	**Placebo N = 1015 n (%)**
During treatment				
Number assessed	1017	1012	1006	1006
Suicidal behavior and/or ideation	27 (2.7)	15 (1.5)	20 (2.0)	25 (2.5)
Suicidal behavior	0	1 (0.1)	0	2 (0.2)
Suicidal ideation	27 (2.7)	15 (1.5)	20 (2.0)	25 (2.5)
During follow up				
Number assessed	833	836	824	791
Suicidal behavior and/or ideation	14 (1.7)	4 (0.5)	9 (1.1)	11 (1.4)
Suicidal behavior	1 (0.1)	0	1 (0.1)	1 (0.1)
Suicidal ideation	14 (1.7)	4 (0.5)	9 (1.1)	11 (1.4)

NRT=Nicotine replacement therapy patch

There were no completed suicides reported in the psychiatric cohort.

The most commonly reported adverse events in subjects treated with CHAMPIX in this study were similar to those observed in premarketing studies. Adverse events reported in ≥10% of

subjects treated with CHAMPIX in the entire study population were nausea (25.3% vs. 6.8% on placebo) and headache (12.2% vs. 9.9% on placebo).

In both cohorts, subjects treated with CHAMPIX had a superior rate of CO-confirmed abstinence during weeks 9 through 12 and 9 through 24 compared to subjects treated with bupropion, nicotine patch and placebo.

The key efficacy results are summarized in the following table:

	Non-psychiatric Cohort	**Psychiatric Cohort**
CAR 9-12 n/N (%)		
CHAMPIX	382/1005 (38.0%)	301/1032 (29.2%)
Bupropion	261/1001 (26.1%)	199/1033 (19.3%)
NRT	267/1013 (26.4%)	209/1025 (20.4%)
Placebo	138/1009 (13.7%)	117/1026 (11.4%)
Treatment Comparisons: Odds ratio (95% CI), p value		
CHAMPIX vs. Placebo	4.00 (3.20, 5.00), P<0.0001	3.24 (2.56, 4.11) , P<0.0001
Bupropion vs. Placebo	2.26 (1.80, 2.85) , P<0.0001	1.87 (1.46, 2.39) , P<0.0001
NRT vs. Placebo	2.30 (1.83, 2.90) , P<0.0001	2.00 (1.56, 2.55) , P<0.0001
CHAMPIX vs. Bupropion	1.77 (1.46, 2.14) , P<0.0001	1.74 (1.41, 2.14) , P<0.0001
CHAMPIX vs. NRT	1.74 (1.43, 2.10) , P<0.0001	1.62 (1.32, 1.99) , P<0.0001
CAR 9-24 n/N (%)		
CHAMPIX	256/1005 (25.5%)	189/1032 (18.3%)
Bupropion	188/1001 (18.8%)	142/1033 (13.7%)
NRT	187/1013 (18.5%)	133/1025 (13.0%)
Placebo	106/1009 (10.5%)	85/1026 (8.3%)
Treatment Comparisons: Odds ratio (95% CI), p value		
CHAMPIX vs. Placebo	2.99 (2.33, 3.83), P<0.0001	2.50 (1.90, 3.29) , P<0.0001
Bupropion vs. Placebo	2.00 (1.54, 2.59), P<0.0001	1.77 (1.33, 2.36) , P<0.0001
NRT vs. Placebo	1.96 (1.51, 2.54), P<0.0001	1.65 (1.24, 2.20), P=0.0007
CHAMPIX vs. Bupropion	1.49 (1.20, 1.85) P=0.0003	1.41 (1.11, 1.79), P=0.0047
CHAMPIX vs. NRT	1.52 (1.23, 1.89), P=0.0001	1.51 (1.19, 1.93), P=0.0008

CAR=continuous abstinence rate; CI=confidence interval; NRT=Nicotine replacement therapy patch

Flexibility in Setting a Quit Date:

The effect of CHAMPIX 1 mg BID in a flexible, patient-selected quit date setting was assessed in a double-blind, placebo-controlled study of 651 subjects. Subjects were randomized 3:1 to CHAMPIX or placebo for a treatment of 12 weeks and a followed up post-treatment for another 12 weeks. In this study, 486 subjects received CHAMPIX and 165 received placebo. Patients were instructed to select a quit date after the initial week of dose titration and before the clinical visit at the end of week 5 of treatment. Patients treated with CHAMPIX had a superior rate of CO-confirmed abstinence during weeks 9 through 12 (53.94%) compared to patients treated with placebo (19.4%) (odds ratio 6.03; 95% CI 3.80, 9.56; p <0.0001) and from week 9 through 24 (35.2%) compared to subjects treated with placebo (12.73%) (odds ratio 4.45; 95% CI 2.62, 7.55; p <0.0001). Adverse events in this study were quantitatively and qualitatively similar to those observed in premarketing studies.

The key results are summarized in the following table:

	CHAMPIX n = 486	Placebo n = 165	Odds ratio (95% CI), p value
CA wk 9-12	53.9%	19.4%	6.03 (3.80, 9.56) p <0.0001
CA wk 9-24	35.2%	12.7%	4.45 (2.62, 7.55) p <0.0001

Neuropsychiatric Safety Meta-analyses and Observational Studies:

Analyses of clinical trial data did not show evidence of an increased risk of serious neuropsychiatric events with varenicline compared to placebo. In addition, independent observational studies have not supported an increased risk of serious neuropsychiatric events in patients treated with varenicline compared to patients prescribed NRT or bupropion.

Analyses of Clinical Trials:

A meta-analysis of 5 randomized, double-blind, placebo-controlled trials, including 1,907 patients (1,130 CHAMPIX, 777 placebo), was conducted to assess suicidal ideation and behavior as reported on the Columbia-Suicide Severity Rating Scale (C-SSRS). This meta-analysis included one trial (N = 127) in patients with a history of schizophrenia or schizoaffective disorder and another trial (N = 525) in patients with a history of depression. The results showed no increase in the incidence of suicidal ideation and/or behavior in patients treated with varenicline compared to patients treated with placebo, with a Risk Ratio (RR) of 0.79 (95% Confidence Interval [CI]: 0.46, 1.36), as shown in the table below. Forty-eight (48) of the 55 patients who reported suicidal ideation or behavior (24 CHAMPIX, 24 placebo) were from the two trials that enrolled patients with a history of schizophrenia, schizoaffective disorder, or depression. Few patients reported these events in the other three trials (4 CHAMPIX, 3 placebo).

Number of Patients and Risk Ratio for Suicidal Ideation and/or Behavior Reported on C-SSRS from a Meta-analysis of 5 Clinical Trials Comparing CHAMPIX to Placebo:

	CHAMPIX (N = 1,130)	**Placebo** (N = 777)
Patients with suicidal ideation and/or behavior* [n (%)]**	28 (2.5)	27 (3.5)
Patient-years of exposure	325	217
Risk ratio # (RR; 95% CI)	0.79 (0.46, 1.36)	

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

A meta-analysis of 18 double-blind, randomized, placebo-controlled clinical trials was conducted to assess the neuropsychiatric safety of CHAMPIX. These trials included the 5 trials described above that used the C-SSRS, and a total of 8,521 patients (5,072 CHAMPIX, 3,449 placebo), some of which had psychiatric conditions. The results showed a similar incidence of combined neuropsychiatric adverse events, other than sleep disorders, in patients treated with CHAMPIX compared to patients treated with placebo, with a risk ratio (RR) of 1.01 (95% CI: 0.88, 1.15).

Pooled data from these 18 trials showed a similar incidence rate of individual categories of psychiatric events in patients treated with CHAMPIX compared to patients treated with placebo. The table below describes the most frequently (≥1%) reported categories of adverse events related to psychiatric safety other than sleep disorders and disturbances.

Psychiatric Adverse Events Occurring in ≥1% of Patients from Pooled Data from 18 Clinical Trials:

	CHAMPIX (N = 5,072)	**Placebo** (N = 3,449)
Anxiety disorders and symptoms	253 (5.0)	206 (6.0)
Depressed mood disorders and disturbances	179 (3.5)	108 (3.1)
Mood disorders and disturbances NEC*	116 (2.3)	53 (1.5)

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

Observational Studies:

Four observational studies, each including 10,000 to 30,000 users of CHAMPIX in the adjusted analyses, compared the risk of serious neuropsychiatric events, including neuropsychiatric hospitalizations and fatal and non-fatal self-harm, in patients treated with CHAMPIX versus patients prescribed NRT or bupropion. All studies were retrospective cohort studies and included patients with and without a psychiatric history. All studies used statistical methods to control for confounding factors, including preferential prescribing of CHAMPIX to healthier patients, although there is the possibility of residual confounding.

Two of the studies found no difference in risk of neuropsychiatric hospitalizations between CHAMPIX users and nicotine patch users (Hazard Ratio [HR] 1.14; 95% Confidence Interval [CI]: 0.56–2.34 in the first study, and 0.76; 95% CI: 0.40-1.46 in the second study). The power to detect differences in these two studies was limited. The third study reported no difference in risk of psychiatric adverse events diagnosed during an emergency department visit or inpatient admission between CHAMPIX users and bupropion users (HR 0.85; 95% CI: 0.55-1.30). Based on post-marketing reports, bupropion may be associated with neuropsychiatric adverse events. The fourth study showed no evidence of a higher risk of fatal and non-fatal self-harm (HR of 0.88; 95% CI: 0.52-1.49) in patients prescribed CHAMPIX compared to patients prescribed NRT. The occurrence of detected suicide was rare during the three months after patients initiated any drug treatment (two cases in 31,260 CHAMPIX users and six cases in 81,545 NRT users).

Other Observational Studies:

Pregnancy Cohort Study:

A population-based cohort study compared infants exposed to CHAMPIX *in utero* (N=335) with infants born to mothers who smoked during pregnancy (N=78,412) and infants born to non-smoking mothers (N=806,438). In this study, infants exposed to CHAMPIX *in utero* were no more likely to have major congenital malformations (3.6%) than infants born to mothers who

smoked during pregnancy (4.3%) or to non-smoking mothers (4.2%). Similarly, infants exposed to CHAMPIX *in utero,* as compared to infants of smoking and non-smoking mothers, were not at increased risk of stillbirth, (0.3%, 0.5%, 0.3%, respectively), small for gestational age (12.5%, 17.1%, 9.1%), preterm birth (7.5%, 7.9%, 5.8%), or premature rupture of membrane (3.6%, 5.4%, 3.8%) (see section **4.6 Fertility, pregnancy and lactation**).

Pediatric population:

The efficacy and safety of varenicline was evaluated in a randomized, double-blind, placebo-controlled study of 312 patients aged 12 to 19 years, who smoked an average of at least 5 cigarettes per day during the 30 days prior to recruitment, and had a score of at least 4 on the Fagerstrom Test for Nicotine Dependence scale. Patients were stratified by age (12 to 16 years of age and 17 to 19 years of age) and by body weight (≤55 kg and >55 kg). Following two week titration, patients randomized to varenicline with a body weight >55 kg received 1 mg twice daily (high dose group) or 0.5 mg twice daily (low dose group), while patients with a body weight ≤55 kg received 0.5 mg twice daily (high dose group) or 0.5 mg once daily (low dose group). Patients received treatment for 12 weeks, followed by a non-treatment period of 40 weeks, along with age-appropriate counseling throughout the study.

Results from this study showed that neither varenicline dose significantly increased continuous abstinence rates at weeks 9 through 12 of treatment compared with placebo in subject 12 to 19 years of age or in subjects 12 to 16 years of age. The study was not powered to assess efficacy in adolescent smokers 17 to 19 years of age, and in this group conclusions cannot be drawn. The varenicline safety profile in this study was consistent with that shown in adult studies. (See section **4.2 Posology and method of administration** – *Use in pediatric patients*)

5.2 Pharmacokinetic properties

Absorption:

Maximum plasma concentrations of varenicline occur typically within 3-4 hours after oral administration. Following administration of multiple oral doses of varenicline, steady-state conditions were reached within 4 days. Over the recommended dosing range, varenicline exhibits linear pharmacokinetics after single or repeated doses. In a mass balance study, absorption of varenicline was virtually complete after oral administration and systemic availability was high. Oral bioavailability of varenicline is unaffected by food or time-of-day dosing.

Distribution:

Varenicline distributes into tissues, including the brain. Apparent volume of distribution averaged 415 liters (%CV = 50) at steady-state. Plasma protein binding of varenicline is low (≤20%) and independent of both age and renal function.

Metabolism:

Varenicline undergoes minimal metabolism with 92% excreted unchanged in the urine and less than 10% excreted as metabolites. Minor metabolites in urine include varenicline N-carbamoylglucuronide and hydroxyvarenicline. In circulation, varenicline comprises 91% of drug-related material. Minor circulating metabolites include varenicline N-carbamoylglucuronide and N-glucosylvarenicline.

Elimination:

The elimination half-life of varenicline is approximately 24 hours. Renal elimination of varenicline is primarily through glomerular filtration along with active tubular secretion possibly via the organic cation transporter, OCT2.

Linearity/Non-linearity:

Varenicline exhibits linear kinetics when given as single (0.1 to 3 mg) or repeated (1 to 3 mg/day) doses.

Pharmacokinetics in special patient populations:

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

Patients with hepatic impairment:

Due to the absence of significant hepatic metabolism, varenicline pharmacokinetics should be unaffected in patients with hepatic impairment (see section **4.2 Posology and method of administration** – *Patients with hepatic impairment*).

Patients with renal insufficiency:

Varenicline pharmacokinetics were 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 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 was increased 2.1-fold. In subjects with end-stage-renal disease (ESRD), varenicline was efficiently removed by hemodialysis (see section **4.2 Posology and method of administration -** *Patients with renal insufficiency*).

Use in elderly patients:

The pharmacokinetics of varenicline in elderly patients with normal renal function (aged 65-75 years) is similar to that of younger adult subjects. In elderly patients with severe renal impairment, dosage adjustment is recommended (see section **4.2 Posology and method of administration** – *Patients with renal insufficiency*).

5.3 Preclinical safety data

Carcinogenesis, Mutagenesis, Impairment of Fertility

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 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) were increased at the mid dose (1 tumor, 5 mg/kg/day, 23 times the maximum recommended human daily exposure based on AUC) and 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.

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.

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 mg twice daily). 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 mg twice daily). 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 mg twice daily).

Teratogenesis

Varenicline succinate was not teratogenic in rats and rabbits at oral doses up to 15 and 30 mg/kg/day, respectively (36- and 50-times the maximum recommended human daily exposure based on AUC at 1 mg twice daily, respectively).

Non-teratogenic 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 mg twice

daily); 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 mg twice daily).

Non-clinical data indicate varenicline has reinforcing properties albeit with lower potency than nicotine. Moreover, in clinical studies in humans, varenicline showed low abuse potential.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline Cellulose; Dibasic Calcium Phosphate, anhydrous; Croscarmellose Sodium; Colloidal Silicon Dioxide; Magnesium Stearate; Opadry® White (0.5 mg tablets); Opadry® Blue (1.0 mg tablets); Opadry® Clear; Purified Water

6.2 Incompatibilities

Not Applicable

6.3 Shelf-life

Refer to expiry date on outer pack.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

CHAMPIX Tablet Starter Pack

Aclar/PVC/blisters with aluminium foil backing in an initial starter pack containing one blister of 11 x 0.5 mg film-coated tablets and a second blister of 14 x 1 mg film-coated tablets in secondary heat sealed card packaging.

CHAMPIX Tablet 1 mg

Aclar/PVC blisters with aluminium foil backing in a pack containing 28 x 1 mg film-coated tablets in secondary heat sealed card packaging.

Aclar/PVC blisters with aluminium foil backing in a pack containing 56 x 1 mg film-coated tablets in secondary heat sealed card packaging.

Not all pack sizes may be marketed locally.

7 PRODUCT OWNER

Pfizer Inc.
235 East 42nd Street
New York 10017
United States

CHA-SIN-0818/1
Date of last revision: January 2019

MEDICATION GUIDE
CHAMPIX®
(Varenicline) Tablets

Read the Medication Guide that comes with CHAMPIX before you start taking it and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your condition or treatment.

What is the most important information I should know about CHAMPIX?

Some people have had serious side effects while using CHAMPIX to help them quit smoking including: New or worse mental health problems, such as changes in behavior, hostility, agitation, depressed mood, and suicidal thoughts or actions. Some people had these symptoms when they began taking CHAMPIX, and others developed them after several weeks of treatment, or after stopping CHAMPIX.

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.

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

- 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 or mood

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.

See "**What are the possible side effects of CHAMPIX?**" for more information about other side effects.

What is CHAMPIX?

CHAMPIX is a prescription medicine to help people stop smoking.

Quitting smoking can lower your chances of having lung disease, heart disease or getting certain types of cancer that are related to smoking.

It is not known if CHAMPIX is safe and effective in children. It is not known if CHAMPIX is safe and effective when used with other stop smoking medicines.

Who should not take CHAMPIX?

Do not take CHAMPIX if you have had a serious allergic or skin reaction to CHAMPIX. Symptoms may include:

Swelling of the face, mouth (tongue, lips, gums), throat or neck

Trouble breathing

Rash, with peeling skin

Blisters in your mouth

What should I tell my doctor before taking CHAMPIX?

See “What is the most important information I should know about CHAMPIX?”

Before you take CHAMPIX, tell your doctor if you:

- use other treatments to quit smoking. Using CHAMPIX with a nicotine patch may cause nausea, vomiting, headache, dizziness, upset stomach, and tiredness to happen more often than if you just use a nicotine patch alone.
- have kidney problems or get kidney dialysis. Your doctor may prescribe a lower dose of CHAMPIX for you.
- have a history of seizures.
- drink alcohol.
- have heart or blood vessel problems.
- have any other medical conditions.
- are pregnant or plan to become pregnant. It is not known if CHAMPIX will harm your unborn baby.
- are breastfeeding. It is not known if CHAMPIX passes into breast milk. If you breastfeed and take CHAMPIX, monitor your baby for seizures as well as spitting up or vomiting more than normal.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins and herbal supplements. Your doctor may need to change the dose of some of your medicines when you stop smoking.

You should not use CHAMPIX while using other medicines to quit smoking. Tell your doctor if you use other treatments to quit smoking.

Know the medicines you take. Keep a list of them with you to show your doctor and

pharmacist when you get a new medicine.

How should I take CHAMPIX?

- There are 3 ways that you can use CHAMPIX to help you quit smoking. Talk to your doctor about the following 3 ways to use CHAMPIX.

1. Choose a **quit date** when you will stop smoking. Start taking CHAMPIX 1 week (7 days) before your **quit date**. **Take CHAMPIX for 12 weeks.**

OR

2. Start taking CHAMPIX before you choose a **quit date**. Pick a date to quit smoking that is between days 8 and 35 of treatment. Take CHAMPIX for 12 weeks.

OR

3. If you are sure that you are not able or willing to quit smoking right away, start taking CHAMPIX and reduce smoking during the first 12 weeks of treatment, as follows:

Weeks 1 through 4	Reduce your smoking to reach one-half of your starting daily number of cigarettes. Example: If you usually smoke 20 cigarettes each day, reduce your smoking to 10 cigarettes each day during weeks 1 through 4.
Weeks 5 through 8	Reduce your smoking to reach one-quarter of your starting daily number of cigarettes. Example: If you usually smoked 20 cigarettes each day, reduce your smoking to 5 cigarettes each day during weeks 5 through 8.
Weeks 9 through 12	Keep reducing your smoking until you are no longer smoking (you reach zero cigarettes each day).

Aim to quit by the end of the 12th week of treatment, or sooner if you feel ready. Continue to take CHAMPIX for another 12 weeks, for a total of 24 weeks of treatment.

Starting CHAMPIX before your quit date gives CHAMPIX time to build up in your body. You can keep smoking during this time. Take CHAMPIX exactly as prescribed by your doctor.

1. Make sure that you try to stop smoking on your quit date. If you slip-up and smoke, try again. Some people need to take CHAMPIX for a few weeks for CHAMPIX to work best.
2. Most people will take CHAMPIX for up to 12 weeks. If you completely quit smoking by 12 weeks, your doctor may prescribe CHAMPIX for another 12 weeks to help you stay cigarette-free.
3. Take CHAMPIX with a full glass (8 ounces) of water.
4. This dosing schedule may not be right for everyone. Talk to your doctor if you are having side effects such as nausea, strange dream, or sleep problems. Your doctor may want to reduce your dose.
5. If you miss a dose of CHAMPIX, take it as soon as you remember. If it is almost time for your next dose, skip the missed dose. Just take your next dose at your regular time. CHAMPIX comes as a white tablet (0.5 mg) and a blue tablet (1 mg). You start with the white tablet and then usually go to the blue tablet. See the chart below for dosing instructions.

Day 1 to Day 3	• White tablet (0.5 mg) • Take 1 tablet each day
Day 4 to Day 7	• White tablet (0.5 mg) • Take 1 in the morning and 1 in the evening
Day 8 to end of treatment	• Blue tablet (1 mg) • Take 1 in the morning and 1 in the evening

What should I avoid while taking CHAMPIX?

Use caution when driving or operating machinery until you know how CHAMPIX affects you. CHAMPIX may make you feel sleepy, dizzy, or have trouble concentrating, making it hard to drive or perform other activities safely.

- Decrease the amount of alcoholic beverages that you drink during treatment with CHAMPIX until you know if CHAMPIX affects your ability to tolerate alcohol. Some people have experienced the following when drinking alcohol during treatment with CHAMPIX:

- increased drunkenness (intoxication)

- unusual or sometimes aggressive behavior

- no memory of things that have happened

What are the possible side effects of CHAMPIX?

Serious side effects of CHAMPIX may include:

- See "**What is the most important information I should know about CHAMPIX?**"

  Seizures. Some people have had seizures during treatment with CHAMPIX. In most cases, the seizures have happened during the first month of treatment with CHAMPIX. If you have seizure during treatment with CHAMPIX, stop taking CHAMPIX and contact your doctor right away.

- **New or worse heart or blood vessel (cardiovascular) problems,** mostly in people who already have cardiovascular problems. Tell your doctor if you have any changes in symptoms during treatment with CHAMPIX.

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

- 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
- Sleepwalking can happen with CHAMPIX, and can sometimes lead to behavior that is harmful to you or other people, or to property. Stop taking CHAMPIX and tell your doctor if you start sleep walking.
- Allergic reactions can happen with CHAMPIX. Some of these allergic reactions can be life-threatening.
- Serious skin reactions, including rash, swelling, redness, and peeling of the skin. Some of these skin reactions can become life-threatening.
- Stop taking CHAMPIX and get medical help right away if you have any of the following symptoms:

  Swelling of the face, mouth (tongue, lips, and gums), throat or neck, trouble breathing, rash with peeling skin, blisters in your mouth

- The most common side effects of CHAMPIX include:
    - nausea
    - sleep problems (trouble sleeping or vivid, unusual, or strange dreams)
    - constipation
    - gas
    - vomiting

Tell your doctor about side effects that bother you or that do not go away.

These are not all the side effects of CHAMPIX. Ask your doctor or pharmacist for more information.

Call your doctor for medical advice about side effects.

How should I store CHAMPIX?

- Do not store CHAMPIX above 30°C.

- **Keep CHAMPIX and all medicines out of the reach of children.**

General information about the safe and effective use of CHAMPIX

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use CHAMPIX **for a condition for which it was not prescribed. Do not give your** CHAMPIX **to other people, even if they have the same symptoms that you have. It may harm them.**

If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about CHAMPIX that is written for healthcare professionals. If you are motivated to quit smoking and did not succeed during prior CHAMPIX treatment for reasons other than side effects, or if you returned to smoking after treatment, speak with your doctor about whether another course of CHAMPIX therapy may be right for you.

What are the ingredients in CHAMPIX?

Active ingredient: varenicline tartrate

Inactive ingredients: microcrystalline cellulose, anhydrous dibasic calcium phosphate, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, Opadry® White (for 0.5 mg), Opadry® Blue (for 1 mg), and Opadry® Clear (for both 0.5 mg and 1 mg)

Rx only

CHA-SIN-0517/PIL/1

Date of last revision: 12 December 2017