CHAMPIX™

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

Varenicline is indicated for smoking cessation.

4.2 Posology and method of administration

Smoking cessation therapies are more likely to succeed for patients who are motivated to stop smoking and who are provided with additional advice and support.

The recommended dose of varenicline 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

The patient should set a date to stop smoking. Varenicline dosing should start 1 week before this date. Alternatively, a flexible approach to quitting may be adopted: the patient can begin varenicline dosing and then quit smoking between Days 8 and 35 of treatment (see section 5.1 Pharmacodynamic properties – *Flexibility in Setting a Quit Date*).

Patients should be treated with varenicline for 12 weeks.

For patients who have successfully stopped smoking at the end of 12 weeks, an additional course of 12 weeks treatment with varenicline 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 varenicline 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 varenicline 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 are motivated to quit and who did not succeed in stopping smoking during prior varenicline therapy, or who relapsed after treatment, should be encouraged to make another attempt with varenicline (see section 5.1 Pharmacodynamic properties - *Study in Subjects Re-treated with Varenicline*).

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

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

Patients with renal insufficiency:
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 with severe renal impairment (estimated creatinine clearance <30 ml/min), the recommended dose of varenicline is 1 mg once daily. 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:

Varenicline is not recommended for use in pediatric patients because its efficacy in this population was not demonstrated (see section 5.1 Pharmacodynamic properties – *Pediatric population* and section 5.2 Pharmacokinetic properties – *Use in pediatric patients*).

4.3 Contraindications

Known hypersensitivity to varenicline or to any of the excipients in the product.

4.4 Special warnings and precautions for use

Effect of smoking cessation: Physiological changes resulting from smoking cessation, with or without treatment with varenicline, may alter the pharmacokinetics or pharmacodynamics of some medicinal products, 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 varenicline was associated with an increase in irritability, urge to smoke, depression, and/or insomnia in up to 3% of patients.

There have been post-marketing reports of neuropsychiatric symptoms, some serious, including changes in behavior or thinking, anxiety, psychosis, mood swings, aggressive behavior, agitation, depressed mood, suicidal ideation and suicidal behavior, in patients attempting to quit smoking with varenicline (see section 4.8 Undesirable effects).

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 varenicline, 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 varenicline 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 varenicline has not been established. Physicians should observe patients attempting to quit smoking with or without varenicline for the occurrence of serious neuropsychiatric symptoms and should instruct patients to contact a healthcare professional if they experience such symptoms.

In clinical trials and post-marketing experience there have been reports of seizures in patients with or without a history of seizures, treated with varenicline. Varenicline 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 varenicline use has not been established.

There have been post-marketing reports of hypersensitivity reactions including angioedema in patients treated with varenicline. Clinical signs included swelling of the face, mouth (tongue, lips, and gums), neck (throat 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 discontinue treatment with varenicline and contact a healthcare provider immediately.

There have also been post-marketing reports of rare but severe cutaneous reactions, including Stevens-Johnson Syndrome and Erythema Multiforme in patients using varenicline. As these skin reactions can be life-threatening, patients should discontinue treatment at the first sign of rash or skin reaction and contact a health care provider immediately.

In a smoking cessation study in patients with stable cardiovascular (CV) disease and in a meta-analysis of 15 clinical trials, some CV events were reported more frequently in patients treated with varenicline compared to placebo. These events occurred primarily in patients with known CV disease. No causal relationship between these events and varenicline 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 varenicline compared to placebo. In these studies, major CV events were infrequent overall and all-cause and CV mortality was lower in patients treated with varenicline compared to patients treated with placebo. Smoking is an independent and major risk factor for CV disease. Patients should be instructed to notify their healthcare providers of new or worsening cardiovascular symptoms and to seek immediate medical attention if they experience signs and symptoms of myocardial infarction or stroke (see section 5.1 Pharmacodynamic properties – *Study in Subjects with Cardiovascular Disease, Cardiac Assessment Study*).

4.5 Interaction with other medicinal products and other forms of interaction

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

In vitro studies indicate that varenicline is unlikely to alter the pharmacokinetics of compounds that are primarily metabolized by cytochrome P450 enzymes.

In vitro studies demonstrate that varenicline does not inhibit cytochrome P450 enzymes (IC_{50} >6,400 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 was shown to not induce the activity of cytochrome P450 enzymes 1A2 and 3A4. Therefore, varenicline is unlikely to alter the pharmacokinetics of compounds that are primarily metabolised by cytochrome P450 enzymes.

In vitro studies demonstrate that active renal secretion of varenicline is mediated by the human organic cation transporter, OCT2. Co-administration with inhibitors of OCT2 does not require a dose adjustment of varenicline as the increase in systemic exposure to varenicline tartrate is not expected to be clinically meaningful (see *Cimetidine* interaction below). Furthermore since metabolism of varenicline represents less than 10% of its clearance, active substances known to affect the cytochrome P450 system are unlikely to alter the pharmacokinetics of varenicline (see section 5.2 Pharmacokinetic properties - *Metabolism*) and therefore a dose adjustment of varenicline would not be required.

In vitro studies demonstrate that varenicline does not inhibit human renal transport proteins at therapeutic concentrations. Therefore, medicinal products that are cleared by renal secretion (e.g., metformin – see below) are unlikely to be affected by varenicline.

Metformin: Varenicline (1 mg twice daily) did not affect the pharmacokinetics of metformin (500 mg twice daily), which is a substrate of OCT2. Metformin had no effect on varenicline pharmacokinetics.

Cimetidine: Co-administration of an OCT2 inhibitor, cimetidine (300 mg four times daily), with varenicline (2 mg single dose) increased the systemic exposure of varenicline by 29% 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.

Warfarin: Varenicline (1 mg twice daily) did not alter the pharmacokinetics of a single 25 mg dose of (R,S) warfarin. 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 varenicline. 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).

Nicotine replacement therapy (NRT): When varenicline (1 mg twice daily) and NRT (transdermal 21 mg/day) were co-administered to smokers (N=24) 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 was greater for the combination than for NRT alone.

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

4.6 Fertility, pregnancy and lactation

Pregnancy:

A moderate amount of data on pregnant women (between 300-1,000 pregnancy outcomes) indicated no malformative or fetal/neonatal toxicity of varenicline (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 varenicline during pregnancy (see section 5.1 Pharmacodynamic properties).

Lactation:

It is unknown whether varenicline is excreted in human breast milk. Animal studies suggest that varenicline is excreted in breast milk. A decision on whether to discontinue breast-feeding or to discontinue therapy with varenicline should be made taking into account the benefit of breast-feeding to the child and the benefit of varenicline therapy to the woman.

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 varenicline 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 varenicline 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 BID 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 varenicline compared with 9.7% for placebo. In this group, the discontinuation rates for the most common adverse events in varenicline 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 varenicline. 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

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
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	

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
Respiratory, thoracic and mediastinal disorders		Dyspnoea; Cough	Upper respiratory tract inflammation; Respiratory tract congestion; Dysphonia; Rhinitis allergic; Throat irritation; Sinus congestion; Upper-airway cough syndrome; Rhinorrhoea	Snoring
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	

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
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%);

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

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%).

4.8.1 Post-marketing Experience:

The following adverse events have been reported during post-approval use of varenicline. 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.

There have been reports of depressed mood, agitation, changes in behavior or thinking, anxiety, psychosis, mood swings, aggressive behavior, suicidal ideation and suicide in patients attempting to quit smoking while taking varenicline (see section 4.4 Special warnings and precautions for use).

There have also been reports of hypersensitivity reactions, such as angioedema and of rare but severe cutaneous reactions, including Stevens-Johnson Syndrome and Erythema Multiforme in patients taking varenicline (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, however, there is no experience in dialysis following overdose (see section 5.2 Pharmacokinetic properties – *Patients with renal insufficiency*).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Varenicline binds with high affinity and selectivity at the $\alpha 4\beta 2$ 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.

Electrophysiology studies *in vitro* and neurochemical studies *in vivo* have shown that varenicline binds to the $\alpha4\beta2$ neuronal nicotinic acetylcholine receptors and stimulates receptor-mediated activity, but at a significantly lower level than nicotine. Nicotine competes for the same human $\alpha4\beta2$ nAChR binding site for which varenicline has higher affinity. Therefore, varenicline can effectively block nicotine's ability to fully activate $\alpha4\beta2$ receptors and the mesolimbic dopamine system, the neuronal mechanism underlying reinforcement and reward experienced upon smoking. Varenicline is highly selective and binds more potently to the $\alpha4\beta2$ receptor subtype (Ki=0.15 nM) than to other common nicotinic receptors ($\alpha3\beta4$ Ki=84 nM, $\alpha7$ Ki=620 nM, $\alpha1\beta\gamma\delta$ Ki=3,400 nM), or to non-nicotinic receptors and transporters (Ki>1 μM, except to 5-HT3 receptors: Ki=350 nM).

The efficacy of varenicline in smoking cessation is a result of varenicline's partial agonist activity at the $\alpha4\beta2$ nicotinic receptor where its binding produces an effect sufficient to alleviate symptoms of craving and withdrawal (agonist activity), while simultaneously resulting in a reduction of the rewarding and reinforcing effects of smoking by preventing nicotine binding to $\alpha4\beta2$ receptors (antagonist activity).

Clinical Efficacy and Safety:

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

Comparative Clinical Studies:

Two identically designed double-blind clinical trials prospectively compared the efficacy of varenicline (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 varenicline 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
Varenicline	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 varenicline in comparison with placebo. Varenicline also significantly reduced reinforcing effects of smoking that can perpetuate smoking behavior in patients who smoke during treatment compared with placebo. The effect of varenicline 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)

Flexibility in Setting a Quit Date:

The effect of varenicline 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 varenicline or placebo for a treatment of 12 weeks and a followed up post-treatment for another 12 weeks. In this study, 486 subjects received varenicline 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 varenicline 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 pre-marketing studies.

The key results are summarized in the following table:

	Varenicline 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

Study in Subjects Re-treated with Varenicline:

Varenicline was evaluated in a double-blind, placebo-controlled trial of 494 patients who had made a previous attempt to quit smoking with varenicline, and either did not succeed in quitting or relapsed after treatment. Subjects were randomized 1:1 to varenicline 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 varenicline 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 varenicline 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:

	Varenicline 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:

Varenicline 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 varenicline 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 varenicline 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 varenicline safety profile in this study was consistent with the pre-marketing studies.

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

Study in Subjects with Cardiovascular Disease:

Varenicline 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 varenicline 1 mg BID or placebo for a treatment of 12 weeks and then were followed for 40 weeks post-treatment. Subjects treated with varenicline 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 warnings and precautions for use).

The key results are summarized in the following table:

	Varenicline 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 varenicline 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 varenicline 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)

	Varenicline N=2016	**Bupropion N=2006**	**NRT N=2022**	**Placebo N=2014**
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 varenicline, 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 varenicline-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:

Varenicline 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 varenicline 1 mg BID or placebo for a treatment of 12 weeks and then were followed for 40 weeks post-treatment. Subjects treated with varenicline 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:

	Varenicline 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:

Varenicline 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 varenicline 1 mg BID or placebo for a treatment of 12 weeks and then followed for 40 weeks post-treatment. Subjects treated with varenicline 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 varenicline 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 (varenicline 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 varenicline and placebo groups and no overall worsening of depression during the study in either treatment group.

The percentage of subjects with suicidal ideation and/or behavior was similar between the varenicline and placebo groups during treatment (6.0% 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 varenicline group.

The key efficacy results are summarized in the following table:

	Varenicline 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

	Varenicline n=256	Placebo n=269	Odds ratio (95% CI), p value
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:
Varenicline 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.

The most common adverse events in subjects taking varenicline 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 varenicline 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 varenicline 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 varenicline-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 varenicline 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 varenicline-treated subject whose lifetime history included several similar attempts. The limited data available from this single smoking cessation study is not sufficient to allow definitive conclusions to be drawn. However, these data do not suggest that varenicline treatment causes or worsens suicidality in subjects with stable schizophrenia or schizoaffective disorder.

Neuropsychiatric Safety Study in Subjects with and without a History of Psychiatric Disorder:
Varenicline 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 varenicline 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			
	Varenicline	**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)

	Non-psychiatric Cohort N=3984			
	Varenicline	**Bupropion**	**NRT**	**Placebo**
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[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[a]	0	0	2 (0.2)	0
Aggression[a]	1 (0.1)	1 (0.1)	0	0
Delusions[a]	0	0	0	0
Hallucinations[a]	0	0	0	0
Homicidal ideation[a]	0	0	0	0
Mania[a]	0	0	0	0
Panic[a]	0	1 (0.1)	1 (0.1)	1 (0.1)
Paranoia[a]	0	0	0	0
Psychosis[a]	0	0	0	0

	Non-psychiatric Cohort N=3984			
	Varenicline	**Bupropion**	**NRT**	**Placebo**
Suicidal behavior[a]	0	1 (0.1)	0	0
Suicidal ideation[a]	0	0	0	1 (0.1)
Completed suicide[a]	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 varenicline, -0.08% (-1.37, 1.21) for bupropion and -0.21% (-1.54, 1.12) for NRT. The use of varenicline, 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			
	Varenicline 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)

	Non-psychiatric Cohort N=3984			
	Varenicline N=990 n (%)	**Bupropion N=989 n (%)**	**NRT N=1006 n (%)**	**Placebo N=999 n (%)**
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			
	Varenicline	**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)	

	Psychiatric Cohort N=4074			
	Varenicline	**Bupropion**	**NRT**	**Placebo**
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)

	Psychiatric Cohort N=4074			
	Varenicline	**Bupropion**	**NRT**	**Placebo**
NPS AE Endpoint Components of severe intensity 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[a]	1 (0.1)	1 (0.1)	4 (0.4)	2 (0.2)
Aggression[a]	1 (0.1)	1 (0.1)	0	1 (0.1)
Delusions[a]	0	0	0	0
Hallucinations[a]	0	1 (0.1)	0	0
Homicidal ideation[a]	0	0	0	0
Mania[a]	2 (0.2)	1 (0.1)	0	0
Panic[a]	0	1 (0.1)	0	1 (0.1)
Paranoia[a]	0	0	0	0
Psychosis[a]	0	1 (0.1)	1 (0.1)	0
Suicidal behavior[a]	1 (0.1)	1 (0.1)	0	1 (0.1)
Suicidal ideation[a]	1 (0.1)	0	1 (0.1)	0
Completed suicide[a]	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 varenicline, 1.78% (-0.24, 3.81) for bupropion and 0.37% (-1.53, 2.26) for NRT. The use of varenicline, 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 varenicline 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 varenicline and placebo groups during treatment and in the non- treatment follow-up, as shown in the following table:

	Psychiatric Cohort N=4074			
	Varenicline 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 varenicline in this study were similar to those observed in premarketing studies. Adverse events reported in ≥10% of subjects treated with varenicline 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 varenicline 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 (%)		
Varenicline	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		
Varenicline 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
Varenicline vs. Bupropion	1.77 (1.46, 2.14) , P<0.0001	1.74 (1.41, 2.14) , P<0.0001
Varenicline 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 (%)		
Varenicline	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		
Varenicline 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
Varenicline vs. Bupropion	1.49 (1.20, 1.85) P=0.0003	1.41 (1.11, 1.79), P=0.0047
Varenicline 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

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 nicotine replacement therapy (NRT) or bupropion.

Analyses of Clinical Trials:

A meta-analysis of 5 randomized, double blind, placebo controlled trials, including 1907 patients (1130 varenicline, 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 varenicline, 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 varenicline, 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 Varenicline to Placebo:

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

* Of 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 varenicline. These trials included the 5 trials described above that used the C-SSRS, and a total of 8521 patients (5072 varenicline, 3449 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 varenicline 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 varenicline 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:

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

* NEC = Not Elsewhere Classified

Counts (percentages) corresponds to the number of patients reporting the event

Observational Studies:

Four observational studies, each including 10,000 to 30,000 users of varenicline 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 varenicline 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 varenicline to healthier patients, although there is the possibility of residual confounding.

Two of the studies found no difference in risk of neuropsychiatric hospitalizations between varenicline 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 varenicline 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 varenicline 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 varenicline users and six cases in 81,545 NRT users).

Other Observational Studies:

Pregnancy Cohort Study:

A population-based cohort study compared infants exposed to varenicline *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 varenicline *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 varenicline *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.

The following table from the above pediatric study shows a comparison of continuous abstinence rates (CAR) from weeks 9-12, confirmed by urine cotinine test, for the full analysis set overall study population and the 12-16 year old population.

CAR 9-12 (%)	Overall n/N (%)	12-to-16-Year Olds n/N (%)
High-Dose Varenicline	22/109 (20.2%)	14/72 (19.4%)
Low-Dose Varenicline	28/103 (27.2%)	25/72 (34.7%)
Placebo	18/100 (18.0%)	13/72 (18.1%)
Treatment Comparisons	**Odds ratio in CAR 9-12 (95% CI) [p-value]**	
High-Dose Varenicline vs. Placebo	1.18 (0.59, 2.37) [0.6337]	1.09 (0.47, 2.53) [0.8339]
Low-Dose Varenicline vs. Placebo	1.73 (0.88, 3.39) [0.1114]	2.42 (1.12, 5.26) [0.0250]*

** This p value is not considered statistically significant. The prespecified statistical testing procedures stopped testing after the high-dose varenicline vs. Placebo treatment comparison in the overall study did not achieve statistical significance.*

CI=confidence interval; N=number of subjects randomised; n=the number of subjects who, at each visit from weeks 9 to 12 (inclusive), reported no smoking and no use of other nicotine-containing products since the last study visit/last contact (on the Nicotine Use Inventory) and at any of these visits were confirmed to have quit based on urine cotinine test.

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 subjects 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* and section 5.2 Pharmacokinetic properties – *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 to healthy volunteers, steady-state conditions were reached within 4 days. Absorption 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:

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.

Excretion:

The elimination half-life of varenicline is approximately 24 hours. Renal elimination of varenicline is primarily through glomerular filtration along with active tubular secretion via the organic cationic 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*).

Use in pediatric patients:

Single and multiple-dose pharmacokinetics of varenicline have been investigated in pediatric patients aged 12 to 17 years old (inclusive) and were approximately dose-proportional over the 0.5 mg to 2 mg daily dose range studied. Steady-state systemic exposure in adolescent patients of bodyweight >55 kg, as assessed by $AUC_{(0-24)}$, was comparable to that noted for the same doses in the adult population. When 0.5 mg BID was given, steady-state daily exposure of varenicline was, on average, higher (by approximately 40%) in adolescent patients with bodyweight $\leq$55 kg compared to that noted in the adult population (see section 4.2 Posology and method of administration – *Use in pediatric patients* and section 5.1 Pharmacodynamic properties – *Pediatric population*).

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 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 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 mg BID).

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 BID, 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 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 mg BID).

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

Core Tablet 0.5 mg/1 mg

Cellulose microcrystalline, calcium hydrogen phosphate anhydrous, croscarmellose sodium, silica colloidal anhydrous, magnesium stearate

Film Coating for 0.5 mg Tablet

Hypromellose, titanium dioxide (E171), macrogols, glycerol triacetate

Film Coating for 1 mg Tablet

Hypromellose, titanium dioxide (E171), macrogols, indigo carmine aluminium lake E132, glycerol triacetate

6.2 Shelf-life

Please see details on carton.

6.3 Special precautions for storage

Store below 30°C.

7. MARKETING AUTHORISATION HOLDER

Pfizer (Thailand) Limited