ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

CHAMPIX 0.5 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet of 4 mm x 8 mm

White, capsular-shaped, biconvex tablets debossed with "*Pfizer*" on one side and "CHX 0.5" on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CHAMPIX is indicated for smoking cessation in adults.

4.2 Posology and method of administration

Posology

The recommended dose is 1 mg varenicline 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. CHAMPIX dosing should usually start at 1-2 weeks before this date (see section 5.1). 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 may be considered for the maintenance of abstinence (see section 5.1).

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).

Patients who are motivated to quit and who did not succeed in stopping smoking during prior CHAMPIX therapy, or who relapsed after treatment, may benefit from another quit attempt with CHAMPIX (see section 5.1).

Patients who cannot tolerate adverse reactions of CHAMPIX may have the dose lowered temporarily or permanently to 0.5 mg twice daily.

In smoking cessation therapy, risk for relapse to smoking is elevated in the period immediately following the end of treatment. In patients with a high risk of relapse, dose tapering may be considered (see section 4.4).

Elderly
No dosage adjustment is necessary for elderly patients (see section 5.2). Because elderly patients are more likely to have decreased renal function, prescribers should consider the renal status of an elderly patient.

Renal impairment
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 moderate renal impairment who experience adverse reactions that are not tolerable, dosing may be reduced to 1 mg once daily.

For patients with severe renal impairment (estimated creatinine clearance < 30 ml/min), the recommended dose of CHAMPIX 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. Based on insufficient clinical experience with CHAMPIX in patients with end stage renal disease, treatment is not recommended in this patient population (see section 5.2).

Hepatic impairment
No dosage adjustment is necessary for patients with hepatic impairment (see section 5.2).

Paediatric population
The safety and efficacy of CHAMPIX in children or adolescents below 18 years have not yet been established. Currently available data are described in section 5.2 but no recommendation on a posology can be made.

Method of administration

CHAMPIX is for oral use and the tablets should be swallowed whole with water.
CHAMPIX can be taken with or without food

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Effect of smoking cessation

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

Neuropsychiatric symptoms

Changes in behaviour or thinking, anxiety, psychosis, mood swings, aggressive behaviour, depression, suicidal ideation and behaviour and suicide attempts have been reported in patients attempting to quit smoking with CHAMPIX in the post-marketing experience.

A large randomised, 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*).

Depressed mood, rarely including suicidal ideation and suicide attempt, may be a symptom of nicotine withdrawal.

Clinicians should be aware of the possible emergence of serious neuropsychiatric symptoms in patients attempting to quit smoking with or without treatment. If serious neuropsychiatric symptoms occur whilst on varenicline treatment, patients should discontinue varenicline immediately and contact a healthcare professional for re-evaluation of treatment.

History of psychiatric disorders

Smoking cessation, with or without pharmacotherapy, has been associated with exacerbation of underlying psychiatric illness (e.g. depression).

CHAMPIX smoking cessation studies have provided data in patients with a history of psychiatric disorders (see section 5.1).

In a smoking cessation clinical trial, neuropsychiatric adverse events were reported more frequently in patients with a history of psychiatric disorders compared to those without a history of psychiatric disorders, regardless of treatment (see section 5.1).

Care should be taken with patients with a history of psychiatric illness and patients should be advised accordingly.

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.

Treatment discontinuation

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. The prescriber should inform the patient accordingly and discuss or consider the need for dose tapering.

Cardiovascular events

Patients taking CHAMPIX should be instructed to notify their doctor 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).

Hypersensitivity reactions

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 health care provider immediately.

Cutaneous reactions

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 healthcare provider immediately.

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 drug interactions. No dosage adjustment of CHAMPIX or co-administered medicinal products listed below is recommended.

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

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) and therefore a dose adjustment of CHAMPIX would not be required.

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

Metformin

Varenicline did not affect the pharmacokinetics of metformin. Metformin had no effect on varenicline pharmacokinetics.

Cimetidine

Co-administration of cimetidine, with varenicline increased the systemic exposure of varenicline by 29% due to a reduction in varenicline renal clearance. No dosage adjustment is recommended based on concomitant cimetidine administration in subjects with normal renal function or in patients with mild to moderate renal impairment. In patients with severe renal impairment, the concomitant use of cimetidine and varenicline should be avoided.

Digoxin

Varenicline did not alter the steady-state pharmacokinetics of digoxin.

Warfarin

Varenicline did not alter the pharmacokinetics of warfarin. Prothrombin time (INR) was not affected by varenicline. Smoking cessation itself may result in changes to warfarin pharmacokinetics (see section 4.4).

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 did not alter the steady-state pharmacokinetics of bupropion.

Nicotine replacement therapy (NRT)
When varenicline and transdermal NRT were co-administered to smokers for 12 days, there was a statistically significant decrease in average systolic blood pressure (mean 2.6 mmHg) measured on the final day of the study. In this study, the incidence of nausea, headache, vomiting, dizziness, dyspepsia, and fatigue was greater for the combination than for NRT alone.

Safety and efficacy of CHAMPIX 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 indicated no malformative or foetal/neonatal toxicity of varenicline (see section 5.1).

Animal studies have shown reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of varenicline during pregnancy (see section 5.1).

Breast-feeding

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 continue/discontinue breast-feeding or to continue/discontinue therapy with CHAMPIX should be made taking into account the benefit of breast-feeding to the child and the benefit of CHAMPIX therapy to the woman.

Fertility

There are no clinical data on the effects of varenicline on fertility.

Non-clinical data revealed no hazard for humans based on standard male and female fertility studies in the rat (see section 5.3).

4.7 Effects on ability to drive and use machines

CHAMPIX may have minor or moderate influence on the ability to drive and use machines. CHAMPIX may cause dizziness and somnolence and therefore may influence the ability to drive and use machines. Patients are advised not to drive, operate complex machinery or engage in other

potentially hazardous activities until it is known whether this medicinal product affects their ability to perform these activities.

4.8 Undesirable effects

Summary of the safety profile

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. No attempt has been made in either the design or the analysis of the CHAMPIX studies to distinguish between adverse reactions associated with study drug treatment or those possibly associated with nicotine withdrawal. Adverse drug reactions are 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.

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.

Tabulated summary of adverse reactions

In the table below all adverse reactions, which occurred at an incidence greater than placebo are listed by system organ class and frequency (very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100) and rare (≥ 1/10,000 to < 1/1,000)). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ Class	Adverse Drug Reactions
Infections and infestations	
Very common	Nasopharyngitis
Common	Bronchitis, sinusitis
Uncommon	Fungal infection, viral infection
Blood and lymphatic system disorders	
Rare	Platelet count decreased
Metabolism and nutrition disorders	
Common	Weight increased, decreased appetite, increased appetite
Uncommon	Hyperglycaemia
Rare	Diabetes mellitus, polydipsia
Psychiatric disorders	
Very common	Abnormal dreams, insomnia
Uncommon	Suicidal ideation, aggression, panic reaction, thinking abnormal, restlessness, mood swings, depression*, anxiety*, hallucinations*, libido increased, libido decreased
Rare	Psychosis, somnambulism, abnormal behaviour, dysphoria, bradyphrenia
Nervous system disorders	
Very common	Headache
Common	Somnolence, dizziness, dysgeusia
Uncommon	Seizure, tremor, lethargy, hypoaesthesia
Rare	Cerebrovascular accident, hypertonia, dysarthria, coordination abnormal, hypogeusia, circadian rhythm sleep disorder

System Organ Class	Adverse Drug Reactions
Eye disorders	
Uncommon	Conjunctivitis, eye pain
Rare	Scotoma, scleral discolouration, mydriasis, photophobia, myopia, lacrimation increased
Ear and labyrinth disorders	
Uncommon	Tinnitus
Cardiac disorders	
Uncommon	Myocardial infarction, angina pectoris, tachycardia, palpitations, heart rate increased
Rare	Atrial fibrillation, electrocardiogram ST segment depression, electrocardiogram T wave amplitude decreased
Vascular disorders	
Uncommon	Blood pressure increased, hot flush
Respiratory, thoracic and mediastinal disorders	
Common	Dyspnoea, cough
Uncommon	Upper respiratory tract inflammation, respiratory tract congestion, dysphonia, rhinitis allergic, throat irritation, sinus congestion, upper-airway cough syndrome, rhinorrhoea
Rare	Laryngeal pain, snoring
Gastrointestinal disorders	
Very common	Nausea
Common	Gastrooesophageal reflux disease, vomiting, constipation, diarrhoea, abdominal distension, abdominal pain, toothache, dyspepsia, flatulence, dry mouth
Uncommon	Haematochezia, gastritis, change of bowel habit, eructation, aphthous stomatitis, gingival pain
Rare	Haematemesis, abnormal faeces, tongue coated
Skin and subcutaneous tissue disorders	
Common	Rash, pruritus
Uncommon	Erythema, acne, hyperhidrosis, night sweats
Rare	Severe cutaneous reactions, including Stevens Johnson Syndrome and Erythema Multiforme, angioedema
Musculoskeletal and connective tissue disorders	
Common	Arthralgia, myalgia, back pain
Uncommon	Muscle spasms, musculoskeletal chest pain
Rare	Joint stiffness, costochondritis
Renal and urinary disorders	
Uncommon	Pollakiuria, nocturia
Rare	Glycosuria, polyuria
Reproductive system and breast disorders	
Uncommon	Menorrhagia
Rare	Vaginal discharge, sexual dysfunction
General disorders and administration site conditions	
Common	Chest pain, fatigue
Uncommon	Chest discomfort, influenza like illness, pyrexia, asthenia, malaise
Rare	Feeling cold, cyst
Investigations	
Common	Liver function test abnormal
Rare	Semen analysis abnormal, C-reactive protein increased, blood calcium decreased
* Frequencies are estimated from a post-marketing, observational cohort study	

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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), however, there is no experience in dialysis following overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other nervous system drugs; Drugs used in addictive disorders; Drugs used in nicotine dependence, ATC code: N07BA03

Mechanism of action

Varenicline binds with high affinity and selectivity at the 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.

Electrophysiology studies *in vitro* and neurochemical studies in vivo have shown that varenicline binds to the α4β2 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 varenicline has higher affinity. Therefore, varenicline can effectively block nicotine's ability to fully activate α4β2 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 α4β2 receptor subtype (Ki=0.15 nM) than to other common nicotinic receptors (α3β4 Ki=84 nM, α7 Ki= 620 nM, α1βγδ Ki= 3,400 nM), or to non-nicotinic receptors and transporters (Ki > 1μM, except to 5-HT3 receptors: Ki=350 nM).

Pharmacodynamic effects

The efficacy of CHAMPIX in smoking cessation is a result of varenicline's partial agonist activity at the α4β2 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 α4β2 receptors (antagonist activity).

Clinical efficacy and safety

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 efficacy of CHAMPIX in smoking cessation was demonstrated in 3 clinical trials involving chronic cigarette smokers (≥ 10 cigarettes per day). Two thousand six hundred nineteen

(2619) patients received CHAMPIX 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 identical 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.

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 CHAMPIX vs. placebo	3.91 $p < 0.0001$	3.13 $p < 0.0001$	3.85 $p < 0.0001$	2.66 $p < 0.0001$
Odds ratio CHAMPIX 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, craving and withdrawal were significantly reduced in patients randomised to CHAMPIX in comparison with placebo. CHAMPIX also significantly reduced reinforcing effects of smoking that can perpetuate smoking behaviour 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 CHAMPIX therapy on the maintenance of abstinence. Patients in this study (n=1,927) received open-label CHAMPIX 1 mg twice daily for 12 weeks. Patients who stopped smoking by Week 12 were then randomised to receive either CHAMPIX (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 CHAMPIX 1 mg twice daily for the maintenance of smoking cessation compared to placebo; superiority to placebo for CA was maintained through week 52. The key results are summarised in the following table:

Continuous Abstinence Rates in Subjects Treated with Champix versus Placebo

	CHAMPIX 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)

*CA: Continuous Abstinence Rate

There is currently limited clinical experience with the use of CHAMPIX among black people to determine clinical efficacy.

Flexible quit date between weeks 1 and 5
The efficacy and safety of varenicline has been evaluated in smokers who had the flexibility of quitting between weeks 1 and 5 of treatment. In this 24-week study, patients received treatment for 12 weeks followed by a 12 week non-treatment follow up phase. The 4 week (week 9-12) CQR for varenicline and placebo was 53.9% and 19.4%, respectively (difference=34.5%, 95% CI: 27.0% - 42.0%) and the CA week 9-24 was 35.2% (varenicline) vs. 12.7% (placebo) (difference=22.5%, 95% CI: 15.8% - 29.1%). Patients who are not willing or able to set the target quit date within 1-2 weeks, could be offered to start treatment and then choose their own quit date within 5 weeks.

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 who experienced an adverse event of a concern during previous treatment were excluded. Subjects were randomised 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 and from weeks 9 through 52 compared to subjects treated with placebo. The key results are summarised in the following table:

Continuous Abstinence Rates in Subjects Treated with Champix versus Placebo

	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

*CA: Continuous Abstinence Rate

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 randomised 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 percent 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; the key results are summarised in the following table:

Continuous Abstinence Rates in Subjects Treated with Champix versus Placebo

	CHAMPIX 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

*CA: Continuous Abstinence Rate

The CHAMPIX safety profile in this study was consistent with that of pre-marketing studies.

Subjects with cardiovascular disease
CHAMPIX was evaluated in a randomised, double-blind, placebo-controlled study of subjects with stable, cardiovascular disease (other than, or in addition to, hypertension) that had been diagnosed for more than 2 months. Subjects were randomised to CHAMPIX 1 mg twice daily (n=353) or placebo (n=350) for 12 weeks and then were followed for 40 weeks post-treatment. The 4 week CQR for varenicline and placebo was 47.3% and 14.3%, respectively and the CA week 9-52 was 19.8% (varenicline) vs. 7.4% (placebo).

Deaths and serious cardiovascular events were adjudicated by a blinded, committee. The following adjudicated events occurred with a frequency ≥ 1% in either treatment group during treatment (or in the 30-day period after treatment): nonfatal myocardial infarction (1.1% vs. 0.3% for CHAMPIX and placebo, respectively), and hospitalisation for angina pectoris (0.6% vs. 1.1%). During non-treatment follow up to 52 weeks, the adjudicated events included need for coronary revascularisation (2.0% vs. 0.6%), hospitalisation 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 revascularisation underwent the procedure as part of management of nonfatal MI and hospitalisation for angina. Cardiovascular death occurred in 0.3% of patients in the CHAMPIX arm and 0.6% of patients in the placebo arm over the course of the 52-week study.

A meta-analysis of 15 clinical trials of ≥ 12 weeks treatment duration, including 7002 patients (4190 CHAMPIX, 2812 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.

The key cardiovascular safety analysis included occurrence and timing of a composite endpoint of Major Adverse Cardiovascular Events (MACE), defined as cardiovascular death, nonfatal MI, and nonfatal stroke. These events included in the endpoint were adjudicated by a blinded, independent committee. Overall, a small number of MACE occurred during treatment in the trials included in the meta-analysis (CHAMPIX 7 [0.17%]; placebo 2 [0.07%]). Additionally, a small number of MACE occurred up to 30 days after treatment (CHAMPIX 13 [0.31%]; placebo 6 [0.21%]).

The meta-analysis showed that exposure to CHAMPIX resulted in a hazard ratio for MACE of 2.83 (95% confidence interval from 0.76 to 10.55, p=0.12) for patients during treatment and 1.95 (95% confidence interval from 0.79 to 4.82, p=0.15) for patients up to 30 days after treatment. These are equivalent to an estimated increase of 6.5 MACE events and 6.3 MACE events per 1,000 patient-years, respectively of exposure. The hazard ratio for MACE was higher in patients with cardiovascular risk factors in addition to smoking compared with that in patients without cardiovascular risk factors other than smoking. There were similar rates of all-cause mortality

(CHAMPIX 6 [0.14%]; placebo 7 [0.25%]) and cardiovascular mortality (CHAMPIX 2 [0.05%]; placebo 2 [0.07%]) in the CHAMPIX arms compared with the placebo arms in the meta-analysis.

Cardiovascular safety assessment study in subjects with and without a history of psychiatric disorder
The cardiovascular (CV) safety of CHAMPIX was evaluated in the Study in Subjects with and without a History of Psychiatric Disorder (parent study; see section 5.1 - *Neuropsychiatric safety*) and its non-treatment extension, the Cardiovascular Safety Assessment Study, which enrolled 4595 of the 6293 subjects who completed the parent study (N=8058) and followed them through week 52. Of all subjects treated in the parent study, 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 events (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.

	CHAMPIX 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)	

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.

Subjects with mild-moderate chronic obstructive pulmonary disease (COPD)
The efficacy and safety of CHAMPIX (1 mg twice daily) for smoking cessation in subjects with mild-moderate COPD was demonstrated in a randomised double-blind placebo-controlled clinical trial. In this 52-week duration study, patients received treatment for 12 weeks, followed by a 40-week non-treatment follow-up phase. The primary endpoint of the study was the CO-confirmed, 4-week Continuous Quit Rate (4W CQR) from week 9 through week 12 and a key secondary endpoint was the Continuous Abstinence (CA) from Week 9 through Week 52. The safety profile of varenicline was comparable to what was reported in other trials in the general population, including pulmonary safety. The results for the 4W CQR (weeks 9 through 12) and CA rate (weeks 9 through 52) are shown in the following table:

	4W CQR	CA Wk 9-52
CHAMPIX, (n = 248)	42.3%	18.5%
Placebo, (n = 251)	8.8%	5.6%
Odds ratio (CHAMPIX vs. Placebo)	8.40 p < 0.0001	4.04 p < 0.0001

Study in subjects with a history of major depressive disorder
The efficacy of varenicline was confirmed in a randomised placebo-controlled trial in 525 subjects with a history of major depression in the past two years or under current stable treatment. The cessation rates in this population were similar to those reported in the general population. Continuous abstinence rate between weeks 9-12 was 35.9% in the varenicline treatment group versus 15.6% in the placebo group (OR 3.35 (95% CI 2.16-5.21)) and between weeks 9-52 was 20.3% versus 10.4% respectively (OR 2.36 (95% CI 1.40-3.98)). 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%). Psychiatric scales showed no differences between the varenicline and placebo groups and no overall worsening of depression, or other psychiatric symptoms, during the study in either treatment group.

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, randomised 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 behaviour prior to enrolment (lifetime history) and after the end of active treatment period (on Days 33 to 85 after the last dose of treatment). 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. Although 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 are not sufficient to allow for definitive conclusions to be drawn about the safety in patients with schizophrenia or schizoaffective disorder.

Neuropsychiatric safety
Study in Subjects with and without a History of Psychiatric Disorder: Varenicline was evaluated in a randomised, 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 randomised 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/or moderate or severe events of agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal ideation, suicidal behaviour or completed suicide.

The following table shows the rates of the composite NPS adverse event primary endpoint by treatment group and the risk differences (RDs) (95% CI) vs placebo in the **non-psychiatric cohort**.

In addition, the table shows the subset of the composite NPS AE endpoint 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)	
Composite NPS AE Endpoint of severe intensity n (%)	1 (0.1)	4 (0.4)	3 (0.3)	5 (0.5)

AE, adverse event; NRT=Nicotine replacement therapy patch

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. The use of varenicline, bupropion and NRT in the non-psychiatric cohort was not associated with a significantly increased risk of NPS adverse events in the composite primary endpoint compared with placebo (95% CIs were lower than or included zero).

The percentage of subjects with suicidal ideation and/or behaviour 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 behaviour and/or ideation	7 (0.7)	4 (0.4)	3 (0.3)	7 (0.7)
Suicidal behaviour	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 behaviour and/or ideation	3 (0.4)	2 (0.2)	3 (0.4)	4 (0.5)

Suicidal behaviour	0	1 (0.1)	0	0
Suicidal ideation	3 (0.4)	2 (0.2)	3 (0.4)	4 (0.5)

NRT=Nicotine replacement therapy patch

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 endpoint by treatment group and the 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 composite NPS AE endpoint 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)	
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 behaviour[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)

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, and the incidence of events in the composite endpoint was higher for each of the active treatments compared to placebo. However, the use of varenicline, bupropion and NRT in the psychiatric cohort was not associated with a significantly increased risk of NPS adverse events in the composite primary endpoint compared with placebo (95% CIs included zero).

In the psychiatric cohort, the percentage of subjects with suicidal ideation and/or behaviour 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 behaviour and/or ideation	27 (2.7)	15 (1.5)	20 (2.0)	25 (2.5)
Suicidal behaviour	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 behaviour and/or ideation	14 (1.7)	4 (0.5)	9 (1.1)	11 (1.4)
Suicidal behaviour	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.

In both cohorts, subjects treated with varenicline demonstrated statistical superiority of CO-confirmed abstinence during weeks 9 through 12 and 9 through 24 compared to subjects treated with bupropion, nicotine patch and placebo (please see table below).

The key efficacy results are summarised in the following table:

	Non-psychiatric Cohort	**Psychiatric Cohort**
CA 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

CA 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

CA = 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.

Treatment discontinuation
The treatment discontinuation rate due to adverse reactions was 11.4% for varenicline compared with 9.7% for placebo. In this group, the discontinuation rates for the most common adverse reactions 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).

Analyses of Clinical Trials:

A meta-analysis of 5 randomised, double-blind, placebo controlled trials, including 1907 patients (1130 varenicline, 777 placebo), was conducted to assess suicidal ideation and behaviour 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 behaviour in patients treated with varenicline compared to patients treated with placebo, as shown in the table below. Of the 55 patients who reported suicidal ideation or behaviour, 48 (24 varenicline, 24 placebo) were from the two trials that enrolled patients with a history of schizophrenia/ schizoaffective disorder, or of 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 Behaviour 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 behaviour* [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 behaviour

** 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, randomised, 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: 0.89-1.15). 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 hospitalisations 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).

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* as compared to infants born to mothers who smoked during pregnancy had lower rates of congenital malformations (3.6% vs 4.3%), stillbirth (0.3% vs 0.5%), preterm birth (7.5% vs 7.9%), small for gestational age (12.5% vs 17.1%), and premature rupture of membrane (3.6% vs 5.4%).

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 litres (%CV= 50) at steady-state. Plasma protein binding of varenicline is low (≤ 20%) and independent of both age and renal function. In rodents, varenicline is transferred through the placenta and excreted in milk.

Biotransformation

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.

In vitro studies demonstrate that varenicline does not inhibit cytochrome P450 enzymes (IC50 > 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.

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 via the organic cationic transporter, OCT2 (see section 4.5).

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 medicinal products, as demonstrated in specific pharmacokinetic studies and in population pharmacokinetic analyses.

Hepatic impairment
Due to the absence of significant hepatic metabolism, varenicline pharmacokinetics should be unaffected in patients with hepatic impairment (see section 4.2).

Renal impairment
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 haemodialysis (see section 4.2).

Elderly
The pharmacokinetics of varenicline in elderly patients with normal renal function (aged 65-75 years) is similar to that of younger adult subjects (see section 4.2). For elderly patients with reduced renal function please refer to section 4.2.

Paediatric population
Single and multiple-dose pharmacokinetics of varenicline have been investigated in paediatric 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 twice daily was given, steady-state daily exposure of varenicline was, on average, higher (by approximately 40%) in adolescent patients with bodyweight ≤ 55 kg compared to that noted in the adult population. Efficacy and safety has not been demonstrated in the paediatric population below 18 years of age and no recommendation on a posology can be made (see section 4.2).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, fertility and embryo-foetal development. In male rats dosed for 2 years with varenicline, there was a dose-related increase in the incidence of hibernoma (tumour of the brown fat). In the offspring of pregnant rats treated with varenicline there were decreases in fertility and increases in the auditory startle response (see section 4.6). These effects were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use. Nonclinical data indicate varenicline has reinforcing properties albeit with lower potency than nicotine. In clinical studies in humans, varenicline showed low abuse potential.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablets' core

Cellulose, Microcrystalline
Calcium Hydrogen Phosphate Anhydrous
Croscarmellose Sodium
Silica, Colloidal Anhydrous
Magnesium Stearate

Film coating

Hypromellose
Titanium Dioxide (E171)
Macrogol 400
Triacetin

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Bottles: 2 years
Blisters: 3 years

6.4 Special precautions for storage

Blisters: Store below 30°C
HDPE Bottle: This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

Maintenance packs

PCTFE/PVC blisters with aluminium foil backing in a pack containing 28 x 0.5 mg film-coated tablets in secondary heat sealed card packaging.

PCTFE/PVC blisters with aluminium foil backing in a pack containing 56 x 0.5 mg film-coated tablets in secondary heat sealed card packaging.

PVC blisters with aluminium foil backing in a pack containing 28 x 0.5 mg film-coated tablets in secondary heat sealed card packaging.

PVC blisters with aluminium foil backing in a pack containing 56 x 0.5 mg film-coated tablets in secondary heat sealed card packaging.

High-density polyethylene (HDPE) bottle with polypropylene child resistant closure and an aluminium foil/polyethylene induction seal containing 56 x 0.5 mg film-coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent
CT13 9NJ
UK

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/360/001
EU/1/06/360/006
EU/1/06/360/007
EU/1/06/360/017
EU/1/06/360/018

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 September 2006
Date of latest renewal: 29 June 2016

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency http://www.ema.europa.eu/

1. NAME OF THE MEDICINAL PRODUCT

CHAMPIX 1 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet of 5 mm x 10 mm

Light blue, capsular-shaped, biconvex tablets debossed with "*Pfizer*" on one side and "CHX 1.0" on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CHAMPIX is indicated for smoking cessation in adults.

4.2 Posology and method of administration

Posology

The recommended dose is 1 mg varenicline 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. CHAMPIX dosing should usually start 1-2 weeks before this date (see section 5.1). 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 may be considered for the maintenance of abstinence (see section 5.1).

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).

Patients who are motivated to quit and who did not succeed in stopping smoking during prior CHAMPIX therapy, or who relapsed after treatment, may benefit from another quit attempt with CHAMPIX (see section 5.1).

Patients who cannot tolerate adverse reactions of CHAMPIX may have the dose lowered temporarily or permanently to 0.5 mg twice daily.

In smoking cessation therapy, risk for relapse to smoking is elevated in the period immediately following the end of treatment. In patients with a high risk of relapse, dose tapering may be considered (see section 4.4).

Elderly
No dosage adjustment is necessary for elderly patients (see section 5.2). Because elderly patients are more likely to have decreased renal function, prescribers should consider the renal status of an elderly patient.

Renal impairment
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 moderate renal impairment who experience adverse reactions that are not tolerable, dosing may be reduced to 1 mg once daily.

For patients with severe renal impairment (estimated creatinine clearance < 30 ml/min), the recommended dose of CHAMPIX 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. Based on insufficient clinical experience with CHAMPIX in patients with end stage renal disease, treatment is not recommended in this patient population (see section 5.2).

Hepatic impairment
No dosage adjustment is necessary for patients with hepatic impairment (see section 5.2).

Paediatric population
The safety and efficacy of CHAMPIX in children or adolescents below 18 years have not yet been established. Currently available data are described in section 5.2 but no recommendation on a posology can be made

Method of administration

CHAMPIX is for oral use and the tablets should be swallowed whole with water.
CHAMPIX can be taken with or without food

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Effect of smoking cessation

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

Neuropsychiatric symptoms

Changes in behaviour or thinking, anxiety, psychosis, mood swings, aggressive behaviour, depression, suicidal ideation and behaviour and suicide attempts have been reported in patients attempting to quit smoking with CHAMPIX in the post-marketing experience.

A large randomised, 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*).

Depressed mood, rarely including suicidal ideation and suicide attempt, may be a symptom of nicotine withdrawal.

Clinicians should be aware of the possible emergence of serious neuropsychiatric symptoms in patients attempting to quit smoking with or without treatment. If serious neuropsychiatric symptoms occur whilst on varenicline treatment, patients should discontinue varenicline immediately and contact a healthcare professional for re-evaluation of treatment.

History of psychiatric disorders
Smoking cessation, with or without pharmacotherapy, has been associated with exacerbation of underlying psychiatric illness (e.g. depression).

CHAMPIX smoking cessation studies have provided data in patients with a history of psychiatric disorders (see section 5.1).

In a smoking cessation clinical trial, neuropsychiatric adverse events were reported more frequently in patients with a history of psychiatric disorders compared to those without a history of psychiatric disorders, regardless of treatment (see section 5.1).

Care should be taken with patients with a history of psychiatric illness and patients should be advised accordingly.

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.

Treatment discontinuation

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. The prescriber should inform the patient accordingly and discuss or consider the need for dose tapering.

Cardiovascular events

Patients taking CHAMPIX should be instructed to notify their doctor 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).

Hypersensitivity reactions

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 health care provider immediately.

Cutaneous reactions

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 healthcare provider immediately.

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 drug interactions. No dosage adjustment of CHAMPIX or co-administered medicinal products listed below is recommended.

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

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) and therefore a dose adjustment of CHAMPIX would not be required.

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

Metformin

Varenicline did not affect the pharmacokinetics of metformin. Metformin had no effect on varenicline pharmacokinetics.

Cimetidine

Co-administration of cimetidine, with varenicline increased the systemic exposure of varenicline by 29% due to a reduction in varenicline renal clearance. No dosage adjustment is recommended based on concomitant cimetidine administration in subjects with normal renal function or in patients with mild to moderate renal impairment. In patients with severe renal impairment, the concomitant use of cimetidine and varenicline should be avoided.

Digoxin

Varenicline did not alter the steady-state pharmacokinetics of digoxin.

Warfarin

Varenicline did not alter the pharmacokinetics of warfarin. Prothrombin time (INR) was not affected by varenicline. Smoking cessation itself may result in changes to warfarin pharmacokinetics (see section 4.4).

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 did not alter the steady-state pharmacokinetics of bupropion.

Nicotine replacement therapy (NRT)
When varenicline and transdermal NRT were co-administered to smokers for 12 days, there was a statistically significant decrease in average systolic blood pressure (mean 2.6 mmHg) measured on the final day of the study. In this study, the incidence of nausea, headache, vomiting, dizziness, dyspepsia, and fatigue was greater for the combination than for NRT alone.

Safety and efficacy of CHAMPIX 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 indicated no malformative or foetal/neonatal toxicity of varenicline (see section 5.1).

Animal studies have shown reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of varenicline during pregnancy (see section 5.1).

Breast-feeding

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 continue/discontinue breast-feeding or to continue/discontinue therapy with CHAMPIX should be made taking into account the benefit of breast-feeding to the child and the benefit of CHAMPIX therapy to the woman.

Fertility

There are no clinical data on the effects of varenicline on fertility.

Non-clinical data revealed no hazard for humans based on standard male and female fertility studies in the rat (see section 5.3).

4.7 Effects on ability to drive and use machines

CHAMPIX may have minor or moderate influence on the ability to drive and use machines. CHAMPIX may cause dizziness and somnolence and therefore may influence the ability to drive and use machines. Patients are advised not to drive, operate complex machinery or engage in other potentially hazardous activities until it is known whether this medicinal product affects their ability to perform these activities.

4.8 Undesirable effects

Summary of the safety profile

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. No attempt has been made in either the design or the analysis of the CHAMPIX studies to distinguish between adverse reactions associated with study drug treatment or those possibly associated with nicotine withdrawal. Adverse drug reactions are 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.

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.

Tabulated summary of adverse reactions

In the table below all adverse reactions, which occurred at an incidence greater than placebo are listed by system organ class and frequency (very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100) and rare (≥ 1/10,000 to < 1/1,000)). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ Class	Adverse Drug Reactions
Infections and infestations	
Very common	Nasopharyngitis
Common	Bronchitis, sinusitis
Uncommon	Fungal infection, viral infection
Blood and lymphatic system disorders	
Rare	Platelet count decreased
Metabolism and nutrition disorders	
Common	Weight increased, decreased appetite, increased appetite
Uncommon	Hyperglycaemia
Rare	Diabetes mellitus, polydipsia
Psychiatric disorders	
Very common	Abnormal dreams, insomnia
Uncommon	Suicidal ideation, aggression, panic reaction, thinking abnormal, restlessness, mood swings, depression*, anxiety*, hallucinations*, libido increased, libido decreased
Rare	Psychosis, somnambulism, abnormal behaviour, dysphoria, bradyphrenia
Nervous system disorders	
Very common	Headache
Common	Somnolence, dizziness, dysgeusia
Uncommon	Seizure, tremor, lethargy, hypoaesthesia
Rare	Cerebrovascular accident, hypertonia, dysarthria, coordination abnormal, hypogeusia, circadian rhythm sleep disorder
Eye disorders	
Uncommon	Conjunctivitis, eye pain
Rare	Scotoma, scleral discolouration, mydriasis, photophobia, myopia, lacrimation increased

System Organ Class	Adverse Drug Reactions
Ear and labyrinth disorders	
Uncommon	Tinnitus
Cardiac disorders	
Uncommon	Myocardial infarction, angina pectoris, tachycardia, palpitations, heart rate increased
Rare	Atrial fibrillation, electrocardiogram ST segment depression, electrocardiogram T wave amplitude decreased
Vascular disorders	
Uncommon	Blood pressure increased, hot flush
Respiratory, thoracic and mediastinal disorders	
Common	Dyspnoea, cough
Uncommon	Upper respiratory tract inflammation, respiratory tract congestion, dysphonia, rhinitis allergic, throat irritation, sinus congestion, upper-airway cough syndrome, rhinorrhoea
Rare	Laryngeal pain, snoring
Gastrointestinal disorders	
Very common	Nausea
Common	Gastrooesophageal reflux disease, vomiting, constipation, diarrhoea, abdominal distension, abdominal pain, toothache, dyspepsia, flatulence, dry mouth
Uncommon	Haematochezia, gastritis, change of bowel habit, eructation, aphthous stomatitis, gingival pain
Rare	Haematemesis, abnormal faeces, tongue coated
Skin and subcutaneous tissue disorders	
Common	Rash, pruritus
Uncommon	Erythema, acne, hyperhidrosis, night sweats
Rare	Severe cutaneous reactions, including Stevens Johnson Syndrome and Erythema Multiforme, angioedema
Musculoskeletal and connective tissue disorders	
Common	Arthralgia, myalgia, back pain
Uncommon	Muscle spasms, musculoskeletal chest pain
Rare	Joint stiffness, costochondritis
Renal and urinary disorders	
Uncommon	Pollakiuria, nocturia
Rare	Glycosuria, polyuria
Reproductive system and breast disorders	
Uncommon	Menorrhagia
Rare	Vaginal discharge, sexual dysfunction
General disorders and administration site conditions	
Common	Chest pain, fatigue
Uncommon	Chest discomfort, influenza like illness, pyrexia, asthenia, malaise
Rare	Feeling cold, cyst
Investigations	
Common	Liver function test abnormal
Rare	Semen analysis abnormal, C-reactive protein increased, blood calcium decreased
* Frequencies are estimated from a post-marketing, observational cohort study	

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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), however, there is no experience in dialysis following overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other nervous system drugs ; Drugs used in addictive disorders, Drugs used in nicotine dependence, ATC code: N07BA03

Mechanism of action

Varenicline binds with high affinity and selectivity at the 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.

Electrophysiology studies *in vitro* and neurochemical studies in vivo have shown that varenicline binds to the α4β2 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 varenicline has higher affinity. Therefore, varenicline can effectively block nicotine's ability to fully activate α4β2 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 α4β2 receptor subtype (Ki=0.15 nM) than to other common nicotinic receptors (α3β4 Ki=84 nM, α7 Ki= 620 nM, α1βγδ Ki= 3,400 nM), or to non-nicotinic receptors and transporters (Ki > 1μM, except to 5-HT3 receptors: Ki=350 nM).

Pharmacodynamic effects

The efficacy of CHAMPIX in smoking cessation is a result of varenicline's partial agonist activity at the α4β2 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 α4β2 receptors (antagonist activity).

Clinical efficacy and safety

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 efficacy of CHAMPIX in smoking cessation was demonstrated in 3 clinical trials involving chronic cigarette smokers (≥ 10 cigarettes per day). Two thousand six hundred nineteen (2619)

patients received CHAMPIX 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 identical 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.

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 CHAMPIX vs. placebo	3.91 $p < 0.0001$	3.13 $p < 0.0001$	3.85 $p < 0.0001$	2.66 $p < 0.0001$
Odds ratio CHAMPIX 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, craving and withdrawal were significantly reduced in patients randomised to CHAMPIX in comparison with placebo. CHAMPIX also significantly reduced reinforcing effects of smoking that can perpetuate smoking behaviour 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 CHAMPIX therapy on the maintenance of abstinence. Patients in this study (n=1,927) received open-label CHAMPIX 1 mg twice daily for 12 weeks. Patients who stopped smoking by Week 12 were then randomised to receive either CHAMPIX (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 CHAMPIX 1 mg twice daily for the maintenance of smoking cessation compared to placebo; superiority to placebo for CA was maintained through week 52. The key results are summarised in the following table:

Continuous Abstinence Rates in Subjects Treated with Champix versus Placebo

	CHAMPIX 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)

*CA: Continuous Abstinence Rate

There is currently limited clinical experience with the use of CHAMPIX among black people to determine clinical efficacy.

Flexible quit date between weeks 1 and 5
The efficacy and safety of varenicline has been evaluated in smokers who had the flexibility of quitting between weeks 1 and 5 of treatment. In this 24-week study, patients received treatment for 12 weeks followed by a 12 week non-treatment follow up phase. The 4 week (week 9-12) CQR for varenicline and placebo was 53.9% and 19.4%, respectively (difference=34.5, 95% CI: 27.0% - 42.0%) and the CA week 9-24 was 35.2% (varenicline) vs. 12.7% (placebo) (difference=22.5%, 95% CI: 15.8% - 29.1%). Patients who are not willing or able to set the target quit date within 1-2 weeks, could be offered to start treatment and then choose their own quit date within 5 weeks.

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 who experienced an adverse event of a concern during previous treatment were excluded. Subjects were randomised 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 and from weeks 9 through 52 compared to subjects treated with placebo. The key results are summarised in the following table:

Continuous Abstinence Rates in Subjects Treated with Champix versus Placebo

	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

*CA: Continuous Abstinence Rate

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 randomised 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 percent 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; the key results are summarised in the following table:

Continuous Abstinence Rates in Subjects Treated with Champix versus Placebo

	CHAMPIX 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

*CA: Continuous Abstinence Rate

The CHAMPIX safety profile in this study was consistent with that of pre-marketing studies.

Subjects with cardiovascular disease
CHAMPIX was evaluated in a randomised, double-blind, placebo-controlled study of subjects with stable, cardiovascular disease (other than, or in addition to, hypertension) that had been diagnosed for more than 2 months. Subjects were randomised to CHAMPIX 1 mg twice daily (n=353) or placebo (n=350) for 12 weeks and then were followed for 40 weeks post-treatment. The 4 week CQR for varenicline and placebo was 47.3% and 14.3%, respectively and the CA week 9-52 was 19.8% (varenicline) vs. 7.4% (placebo).

Deaths and serious cardiovascular events were adjudicated by a blinded, committee. The following adjudicated events occurred with a frequency ≥ 1% in either treatment group during treatment (or in the 30-day period after treatment): nonfatal myocardial infarction (1.1% vs. 0.3% for CHAMPIX and placebo, respectively), and hospitalisation for angina pectoris (0.6% vs. 1.1%). During non-treatment follow up to 52 weeks, the adjudicated events included need for coronary revascularisation (2.0% vs. 0.6%), hospitalisation 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 revascularisation underwent the procedure as part of management of nonfatal MI and hospitalisation for angina. Cardiovascular death occurred in 0.3% of patients in the CHAMPIX arm and 0.6% of patients in the placebo arm over the course of the 52-week study.

A meta-analysis of 15 clinical trials of ≥ 12 weeks treatment duration, including 7002 patients (4190 CHAMPIX, 2812 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.

The key cardiovascular safety analysis included occurrence and timing of a composite endpoint of Major Adverse Cardiovascular Events (MACE), defined as cardiovascular death, nonfatal MI, and nonfatal stroke. These events included in the endpoint were adjudicated by a blinded, independent committee. Overall, a small number of MACE occurred during treatment in the trials included in the meta-analysis (CHAMPIX 7 [0.17%]; placebo 2 [0.07%]). Additionally, a small number of MACE occurred up to 30 days after treatment (CHAMPIX 13 [0.31%]; placebo 6 [0.21%]).

The meta-analysis showed that exposure to CHAMPIX resulted in a hazard ratio for MACE of 2.83 (95% confidence interval from 0.76 to 10.55, p=0.12) for patients during treatment and 1.95 (95% confidence interval from 0.79 to 4.82, p=0.15) for patients up to 30 days after treatment. These are equivalent to an estimated increase of 6.5 MACE events and 6.3 MACE events per 1,000 patient-years, respectively of exposure. The hazard ratio for MACE was higher in patients with cardiovascular risk factors in addition to smoking compared with that in patients without cardiovascular risk factors other than smoking. There were similar rates of all-cause mortality

(CHAMPIX 6 [0.14%]; placebo 7 [0.25%]) and cardiovascular mortality (CHAMPIX 2 [0.05%]; placebo 2 [0.07%]) in the CHAMPIX arms compared with the placebo arms in the meta-analysis.

Cardiovascular safety assessment study in subjects with and without a history of psychiatric disorder
The cardiovascular (CV) safety of CHAMPIX was evaluated in the Study in Subjects with and without a History of Psychiatric Disorder (parent study; see section 5.1 - *Neuropsychiatric safety*) and its non-treatment extension, the Cardiovascular Safety Assessment Study, which enrolled 4595 of the 6293 subjects who completed the parent study (N=8058) and followed them through week 52. Of all subjects treated in the parent study, 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 events (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.

	CHAMPIX 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)	

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.

Subjects with mild-moderate chronic obstructive pulmonary disease (COPD)
The efficacy and safety of CHAMPIX (1 mg twice daily) for smoking cessation in subjects with mild-moderate COPD was demonstrated in a randomised double-blind placebo-controlled clinical trial. In this 52-week duration study, patients received treatment for 12 weeks, followed by a 40-week non-treatment follow-up phase. The primary endpoint of the study was the CO-confirmed, 4-week Continuous Quit Rate (4W CQR) from week 9 through week 12 and a key secondary endpoint was the Continuous Abstinence (CA) from Week 9 through Week 52. The safety profile of varenicline was comparable to what was reported in other trials in the general population, including pulmonary safety. The results for the 4W CQR (weeks 9 through 12) and CA rate (weeks 9 through 52) are shown in the following table:

	4W CQR	CA Wk 9-52
CHAMPIX, (n = 248)	42.3%	18.5%
Placebo, (n = 251)	8.8%	5.6%
Odds ratio (CHAMPIX vs. Placebo)	8.40 p < 0.0001	4.04 p < 0.0001

Study in subjects with a history of major depressive disorder
The efficacy of varenicline was confirmed in a randomised placebo-controlled trial of 525 subjects with a history of major depression in the past two years or under current stable treatment. The cessation rates in this population were similar to those reported in the general population. Continuous abstinence rate between weeks 9-12 was 35.9% in the varenicline treatment group versus 15.6% in the placebo group (OR 3.35 (95% CI 2.16-5.21)) and between weeks 9-52 was 20.3% versus 10.4% respectively (OR 2.36 (95% CI 1.40-3.98)). 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%). Psychiatric scales showed no differences between the varenicline and placebo groups and no overall worsening of depression, or other psychiatric symptoms, during the study in either treatment group.

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, randomised 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 behaviour prior to enrolment (lifetime history) and after the end of active treatment period (on Days 33 to 85 after the last dose of treatment). 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. Although 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 are not sufficient to allow for definitive conclusions to be drawn about the safety in patients with schizophrenia or schizoaffective disorder.

Neuropsychiatric Safety Study in Subjects with and without a History of Psychiatric Disorder:
Varenicline was evaluated in a randomised, 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 randomised 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/or moderate or severe events of agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal ideation, suicidal behaviour or completed suicide.

The following table shows the rates of the composite NPS adverse event primary endpoint by treatment group and the risk differences (RDs) (95% CI) vs placebo in the **non-psychiatric cohort**.

In addition, the table shows the subset of the composite NPS AE endpoint 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)	
Composite NPS AE Endpoint of severe intensity n (%)	1 (0.1)	4 (0.4)	3 (0.3)	5 (0.5)

AE, adverse event; NRT=Nicotine replacement therapy patch

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. The use of varenicline, bupropion and NRT in the non-psychiatric cohort was not associated with a significantly increased risk of NPS adverse events in the composite primary endpoint compared with placebo (95% CIs were lower than or included zero).

The percentage of subjects with suicidal ideation and/or behaviour 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 behaviour and/or ideation	7 (0.7)	4 (0.4)	3 (0.3)	7 (0.7)
Suicidal behaviour	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 behaviour and/or ideation	3 (0.4)	2 (0.2)	3 (0.4)	4 (0.5)
Suicidal behaviour	0	1 (0.1)	0	0
Suicidal ideation	3 (0.4)	2 (0.2)	3 (0.4)	4 (0.5)

NRT=Nicotine replacement therapy patch

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 endpoint by treatment group and the 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 composite NPS AE endpoint 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)	
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 behaviour[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)

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, and the incidence of events in the composite endpoint was higher for each of the active treatments compared to placebo. However, the use of varenicline, bupropion and NRT in the psychiatric cohort was not associated with a significantly increased risk of NPS adverse events in the composite primary endpoint compared with placebo (95% CIs included zero).

In the psychiatric cohort, the percentage of subjects with suicidal ideation and/or behaviour 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 behaviour and/or ideation	27 (2.7)	15 (1.5)	20 (2.0)	25 (2.5)
Suicidal behaviour	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 behaviour and/or ideation	14 (1.7)	4 (0.5)	9 (1.1)	11 (1.4)
Suicidal behaviour	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.

In both cohorts, subjects treated with varenicline demonstrated statistical superiority of CO-confirmed abstinence during weeks 9 through 12 and 9 through 24 compared to subjects treated with bupropion, nicotine patch and placebo (please see table below).

The key efficacy results are summarised in the following table:

	Non-psychiatric Cohort	**Psychiatric Cohort**
CA 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
CA 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

CA = 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.

Treatment discontinuation
The treatment discontinuation rate due to adverse reactions was 11.4% for varenicline compared with 9.7% for placebo. In this group, the discontinuation rates for the most common adverse reactions 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).

Analyses of Clinical Trials:

A meta-analysis of 5 randomised, double-blind, placebo controlled trials, including 1907 patients (1130 varenicline, 777 placebo), was conducted to assess suicidal ideation and behaviour 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 behaviour in patients treated with varenicline compared to patients treated with placebo, as shown in the table below. Of the 55 patients who reported suicidal ideation or behaviour, 48 (24 varenicline, 24 placebo) were from the two trials that enrolled patients with a history of schizophrenia/ schizoaffective disorder, or of 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 Behaviour 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 behaviour* [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 behaviour

** 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, randomised, 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: 0.89-1.15). 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 hospitalisations 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).

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* as compared to infants born to mothers who smoked during pregnancy had lower rates of congenital malformations (3.6% vs 4.3%), stillbirth (0.3% vs 0.5%), preterm birth (7.5% vs 7.9%), small for gestational age (12.5% vs 17.1%), and premature rupture of membrane (3.6% vs 5.4%).

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 litres (%CV= 50) at steady-state. Plasma protein binding of varenicline is low (≤ 20%) and independent of both age and renal function. In rodents, varenicline is transferred through the placenta and excreted in milk.

Biotransformation

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.

In vitro studies demonstrate that varenicline does not inhibit cytochrome P450 enzymes (IC50 > 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.

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 via the organic cationic transporter, OCT2 (see section 4.5).

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 medicinal products, as demonstrated in specific pharmacokinetic studies and in population pharmacokinetic analyses.

Hepatic impairment
Due to the absence of significant hepatic metabolism, varenicline pharmacokinetics should be unaffected in patients with hepatic impairment. (see section 4.2).

Renal impairment
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 haemodialysis (see section 4.2).

Elderly
The pharmacokinetics of varenicline in elderly patients with normal renal function (aged 65-75 years) is similar to that of younger adult subjects (see section 4.2). For elderly patients with reduced renal function please refer to section 4.2.

Paediatric population
Single and multiple-dose pharmacokinetics of varenicline have been investigated in paediatric 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 twice daily was given, steady-state daily exposure of varenicline was, on average, higher (by approximately 40%) in adolescent patients with bodyweight ≤ 55 kg compared to that noted in the adult population. Efficacy and safety has not been demonstrated in the paediatric population below 18 years of age and no recommendation on a posology can be made (see section 4.2).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, fertility and embryo-foetal development. In male rats dosed for 2 years with varenicline, there was a dose-related increase in the incidence of hibernoma (tumour of the brown fat). In the offspring of pregnant rats treated with varenicline there were decreases in fertility and increases in the auditory startle response (see section 4.6). These effects were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use. Nonclinical data indicate varenicline has reinforcing properties albeit with lower potency than nicotine. In clinical studies in humans, varenicline showed low abuse potential.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablets' core

Cellulose, Microcrystalline
Calcium Hydrogen Phosphate Anhydrous
Croscarmellose Sodium
Silica, Colloidal Anhydrous
Magnesium Stearate

Film coating

Hypromellose
Titanium Dioxide (E171)
Macrogol 400
Indigo Carmine Aluminium Lake E132
Triacetin

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Bottles: 2 years
Blisters: 3 years

6.4 Special precautions for storage

Blisters: Store below 30°C

HDPE Bottle: This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

Maintenance packs

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

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

PCTFE/PVC blisters with aluminium foil backing in a pack containing 28 x 1 mg film-coated tablets in a carton.

PCTFE/PVC blisters with aluminium foil backing in a pack containing 56 x 1 mg film-coated tablets in a carton.

PCTFE/PVC blisters with aluminium foil backing in a pack containing 112 x 1 mg film-coated tablets in a carton.

PCTFE/PVC blisters with aluminium foil backing in a pack containing 140 x 1 mg film-coated tablets in a carton.

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

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

PVC blisters with aluminium foil backing in a pack containing 28 x 1 mg film-coated tablets in a carton.

PVC blisters with aluminium foil backing in a pack containing 56 x 1 mg film-coated tablets in a carton.

PVC blisters with aluminium foil backing in a pack containing 112 x 1 mg film-coated tablets in a carton.

PVC blisters with aluminium foil backing in a pack containing 140 x 1 mg film-coated tablets in a carton.

High-density polyethylene (HDPE) bottle with polypropylene child resistant closure and an aluminium foil / polyethylene induction seal containing 56 x 1 mg film-coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent
CT13 9NJ
UK

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/360/002
EU/1/06/360/004
EU/1/06/360/005
EU/1/06/360/009
EU/1/06/360/010
EU/1/06/360/011
EU/1/06/360/013
EU/1/06/360/015
EU/1/06/360/016
EU/1/06/360/020
EU/1/06/360/021
EU/1/06/360/022
EU/1/06/360/024

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 September 2006
Date of latest renewal: 29 June 2016

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency http://www.ema.europa.eu/

1. NAME OF THE MEDICINAL PRODUCT

CHAMPIX 0.5 mg film-coated tablets
CHAMPIX 1 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

0.5 mg film-coated tablets of 4mm x 8mm: White, capsular-shaped, biconvex tablets debossed with "*Pfizer*" on one side and "CHX 0.5" on the other side.

1 mg film-coated tablets of 5mm x 10mm: Light blue, capsular-shaped, biconvex tablets debossed with "*Pfizer*" on one side and "CHX 1.0" on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CHAMPIX is indicated for smoking cessation in adults.

4.2 Posology and method of administration

Posology

The recommended dose is 1 mg varenicline 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. CHAMPIX dosing should usually start at 1-2 weeks before this date (see section 5.1). 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 may be considered for the maintenance of abstinence (see section 5.1).

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).

Patients who are motivated to quit and who did not succeed in stopping smoking during prior CHAMPIX therapy, or who relapsed after treatment, may benefit from another quit attempt with CHAMPIX (see section 5.1).

Patients who cannot tolerate adverse reactions of CHAMPIX may have the dose lowered temporarily or permanently to 0.5 mg twice daily.

In smoking cessation therapy, risk for relapse to smoking is elevated in the period immediately following the end of treatment. In patients with a high risk of relapse, dose tapering may be considered (see section 4.4).

Elderly
No dosage adjustment is necessary for elderly patients (see section 5.2). Because elderly patients are more likely to have decreased renal function, prescribers should consider the renal status of an elderly patient.

Renal impairment
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 moderate renal impairment who experience adverse reactions that are not tolerable, dosing may be reduced to 1 mg once daily.

For patients with severe renal impairment (estimated creatinine clearance < 30 ml/min), the recommended dose of CHAMPIX 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. Based on insufficient clinical experience with CHAMPIX in patients with end stage renal disease, treatment is not recommended in this patient population (see section 5.2).

Hepatic impairment
No dosage adjustment is necessary for patients with hepatic impairment (see section 5.2).

Paediatric population
The safety and efficacy of CHAMPIX in children or adolescents below 18 years have not yet been established. Currently available data are described in section 5.2 but no recommendation on a posology can be made.

Method of administration

CHAMPIX is for oral use and the tablets should be swallowed whole with water.
CHAMPIX can be taken with or without food

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Effect of smoking cessation

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

Neuropsychiatric symptoms

Changes in behaviour or thinking, anxiety, psychosis, mood swings, aggressive behaviour, depression, suicidal ideation and behaviour and suicide attempts have been reported in patients attempting to quit smoking with CHAMPIX in the post-marketing experience.

A large randomised, 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*).

Depressed mood, rarely including suicidal ideation and suicide attempt, may be a symptom of nicotine withdrawal.

Clinicians should be aware of the possible emergence of serious neuropsychiatric symptoms in patients attempting to quit smoking with or without treatment. If serious neuropsychiatric symptoms occur whilst on varenicline treatment, patients should discontinue varenicline immediately and contact a healthcare professional for re-evaluation of treatment.

History of psychiatric disorders

Smoking cessation, with or without pharmacotherapy, has been associated with exacerbation of underlying psychiatric illness (e.g. depression).

CHAMPIX smoking cessation studies have provided data in patients with a history of psychiatric disorders (see section 5.1).

In a smoking cessation clinical trial, neuropsychiatric adverse events were reported more frequently in patients with a history of psychiatric disorders compared to those without a history of psychiatric disorders, regardless of treatment (see section 5.1).

Care should be taken with patients with a history of psychiatric illness and patients should be advised accordingly.

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.

Treatment discontinuation

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. The prescriber should inform the patient accordingly and discuss or consider the need for dose tapering.

Cardiovascular events

Patients taking CHAMPIX should be instructed to notify their doctor 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).

Hypersensitivity reactions

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 health care provider immediately.

Cutaneous reactions

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 healthcare provider immediately.

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 drug interactions. No dosage adjustment of CHAMPIX or co-administered medicinal products listed below is recommended.

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

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) and therefore a dose adjustment of CHAMPIX would not be required.

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

Metformin

Varenicline did not affect the pharmacokinetics of metformin. Metformin had no effect on varenicline pharmacokinetics.

Cimetidine

Co-administration of cimetidine, with varenicline increased the systemic exposure of varenicline by 29% due to a reduction in varenicline renal clearance. No dosage adjustment is recommended based on concomitant cimetidine administration in subjects with normal renal function or in patients with

mild to moderate renal impairment. In patients with severe renal impairment, the concomitant use of cimetidine and varenicline should be avoided.

Digoxin

Varenicline did not alter the steady-state pharmacokinetics of digoxin.

Warfarin

Varenicline did not alter the pharmacokinetics of warfarin. Prothrombin time (INR) was not affected by varenicline. Smoking cessation itself may result in changes to warfarin pharmacokinetics (see section 4.4).

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 did not alter the steady-state pharmacokinetics of bupropion.

Nicotine replacement therapy (NRT)
When varenicline and transdermal NRT were co-administered to smokers for 12 days, there was a statistically significant decrease in average systolic blood pressure (mean 2.6 mmHg) measured on the final day of the study. In this study, the incidence of nausea, headache, vomiting, dizziness, dyspepsia, and fatigue was greater for the combination than for NRT alone.

Safety and efficacy of CHAMPIX 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 indicated no malformative or foetal/neonatal toxicity of varenicline (see section 5.1).

Animal studies have shown reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of varenicline during pregnancy (see section 5.1).

Breast-feeding

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 continue/discontinue breast-feeding or to continue/discontinue therapy with CHAMPIX should be made taking into account the benefit of breast-feeding to the child and the benefit of CHAMPIX therapy to the woman.

Fertility

There are no clinical data on the effects of varenicline on fertility.

Non-clinical data revealed no hazard for humans based on standard male and female fertility studies in the rat (see section 5.3).

4.7 Effects on ability to drive and use machines

CHAMPIX may have minor or moderate influence on the ability to drive and use machines. CHAMPIX may cause dizziness and somnolence and therefore may influence the ability to drive and use machines. Patients are advised not to drive, operate complex machinery or engage in other potentially hazardous activities until it is known whether this medicinal product affects their ability to perform these activities.

4.8 Undesirable effects

Summary of the safety profile

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. No attempt has been made in either the design or the analysis of the CHAMPIX studies to distinguish between adverse reactions associated with study drug treatment or those possibly associated with nicotine withdrawal. Adverse drug reactions are 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.

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.

Tabulated summary of adverse reactions

In the table below all adverse reactions, which occurred at an incidence greater than placebo are listed by system organ class and frequency (very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100) and rare (≥ 1/10,000 to < 1/1,000)). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ Class	Adverse Drug Reactions
Infections and infestations	
Very common	Nasopharyngitis
Common	Bronchitis, sinusitis
Uncommon	Fungal infection, viral infection
Blood and lymphatic system disorders	
Rare	Platelet count decreased
Metabolism and nutrition disorders	
Common	Weight increased, decreased appetite, increased appetite
Uncommon	Hyperglycaemia
Rare	Diabetes mellitus, polydipsia
Psychiatric disorders	
Very common	Abnormal dreams, insomnia
Uncommon	Suicidal ideation, aggression, panic reaction, thinking abnormal, restlessness, mood swings, depression*, anxiety*, hallucinations*, libido increased, libido decreased
Rare	Psychosis, somnambulism, abnormal behaviour, dysphoria, bradyphrenia
Nervous system disorders	
Very common	Headache
Common	Somnolence, dizziness, dysgeusia

System Organ Class	Adverse Drug Reactions
Uncommon	Seizure, tremor, lethargy, hypoaesthesia
Rare	Cerebrovascular accident, hypertonia, dysarthria, coordination abnormal, hypogeusia, circadian rhythm sleep disorder
Eye disorders	
Uncommon	Conjunctivitis, eye pain
Rare	Scotoma, scleral discolouration, mydriasis, photophobia, myopia, lacrimation increased
Ear and labyrinth disorders	
Uncommon	Tinnitus
Cardiac disorders	
Uncommon	Myocardial infarction, angina pectoris, tachycardia, palpitations, heart rate increased
Rare	Atrial fibrillation, electrocardiogram ST segment depression, electrocardiogram T wave amplitude decreased
Vascular disorders	
Uncommon	Blood pressure increased, hot flush
Respiratory, thoracic and mediastinal disorders	
Common	Dyspnoea, cough
Uncommon	Upper respiratory tract inflammation, respiratory tract congestion, dysphonia, rhinitis allergic, throat irritation, sinus congestion, upper-airway cough syndrome, rhinorrhoea
Rare	Laryngeal pain, snoring
Gastrointestinal disorders	
Very common	Nausea
Common	Gastrooesophageal reflux disease, vomiting, constipation, diarrhoea, abdominal distension, abdominal pain, toothache, dyspepsia, flatulence, dry mouth
Uncommon	Haematochezia, gastritis, change of bowel habit, eructation, aphthous stomatitis, gingival pain
Rare	Haematemesis, abnormal faeces, tongue coated
Skin and subcutaneous tissue disorders	
Common	Rash, pruritus
Uncommon	Erythema, acne, hyperhidrosis, night sweats
Rare	Severe cutaneous reactions, including Stevens Johnson Syndrome and Erythema Multiforme, angioedema
Musculoskeletal and connective tissue disorders	
Common	Arthralgia, myalgia, back pain
Uncommon	Muscle spasms, musculoskeletal chest pain
Rare	Joint stiffness, costochondritis
Renal and urinary disorders	
Uncommon	Pollakiuria, nocturia
Rare	Glycosuria, polyuria
Reproductive system and breast disorders	
Uncommon	Menorrhagia
Rare	Vaginal discharge, sexual dysfunction
General disorders and administration site conditions	
Common	Chest pain, fatigue
Uncommon	Chest discomfort, influenza like illness, pyrexia, asthenia, malaise
Rare	Feeling cold, cyst
Investigations	
Common	Liver function test abnormal
Rare	Semen analysis abnormal, C-reactive protein increased, blood calcium decreased
* Frequencies are estimated from a post-marketing, observational cohort study	

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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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), however, there is no experience in dialysis following overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other nervous system drugs; Drugs used in addictive disorders; Drugs used in nicotine dependence, ATC code: N07BA03

Mechanism of action

Varenicline binds with high affinity and selectivity at the 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.

Electrophysiology studies *in vitro* and neurochemical studies in vivo have shown that varenicline binds to the α4β2 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 varenicline has higher affinity. Therefore, varenicline can effectively block nicotine's ability to fully activate α4β2 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 α4β2 receptor subtype (Ki=0.15 nM) than to other common nicotinic receptors (α3β4 Ki=84 nM, α7 Ki= 620 nM, α1βγδ Ki= 3,400 nM), or to non-nicotinic receptors and transporters (Ki > 1μM, except to 5-HT3 receptors: Ki=350 nM).

Pharmacodynamic effects

The efficacy of CHAMPIX in smoking cessation is a result of varenicline's partial agonist activity at the α4β2 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 α4β2 receptors (antagonist activity).

Clinical efficacy and safety

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 efficacy of CHAMPIX in smoking cessation was demonstrated in 3 clinical trials involving chronic cigarette smokers (≥ 10 cigarettes per day). Two thousand six hundred nineteen (2619)

patients received CHAMPIX 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 identical 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.

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 CHAMPIX vs. placebo	3.91 $p < 0.0001$	3.13 $p < 0.0001$	3.85 $p < 0.0001$	2.66 $p < 0.0001$
Odds ratio CHAMPIX 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, craving and withdrawal were significantly reduced in patients randomised to CHAMPIX in comparison with placebo. CHAMPIX also significantly reduced reinforcing effects of smoking that can perpetuate smoking behaviour 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 CHAMPIX therapy on the maintenance of abstinence. Patients in this study (n=1,927) received open-label CHAMPIX 1 mg twice daily for 12 weeks. Patients who stopped smoking by Week 12 were then randomised to receive either CHAMPIX (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 CHAMPIX 1 mg twice daily for the maintenance of smoking cessation compared to placebo; superiority to placebo for CA was maintained through week 52. The key results are summarised in the following table:

Continuous Abstinence Rates in Subjects Treated with Champix versus Placebo

	CHAMPIX 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)

*CA: Continuous Abstinence Rate

There is currently limited clinical experience with the use of CHAMPIX among black people to determine clinical efficacy.

Flexible quit date between weeks 1 and 5
The efficacy and safety of varenicline has been evaluated in smokers who had the flexibility of quitting between weeks 1 and 5 of treatment. In this 24-week study, patients received treatment for 12 weeks followed by a 12 week non-treatment follow up phase. The 4 week (week 9-12) CQR for varenicline and placebo was 53.9% and 19.4%, respectively (difference=34.5%, 95% CI: 27.0% - 42.0%) and the CA week 9-24 was 35.2% (varenicline) vs. 12.7% (placebo) (difference=22.5%, 95% CI: 15.8% - 29.1%). Patients who are not willing or able to set the target quit date within 1-2 weeks, could be offered to start treatment and then choose their own quit date within 5 weeks.

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 who experienced an adverse event of a concern during previous treatment were excluded. Subjects were randomised 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 and from weeks 9 through 52 compared to subjects treated with placebo. The key results are summarised in the following table:

Continuous Abstinence Rates in Subjects Treated with Champix versus Placebo

	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

*CA: Continuous Abstinence

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 randomised 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 percent 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; the key results are summarised in the following table:

Continuous Abstinence Rates in Subjects Treated with Champix versus Placebo

	CHAMPIX 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

*CA: Continuous Abstinence Rate

The CHAMPIX safety profile in this study was consistent with that of pre-marketing studies.

Subjects with cardiovascular disease

CHAMPIX was evaluated in a randomised, double-blind, placebo-controlled study of subjects with stable, cardiovascular disease (other than, or in addition to, hypertension) that had been diagnosed for more than 2 months. Subjects were randomised to CHAMPIX 1 mg twice daily (n=353) or placebo (n=350) for 12 weeks and then were followed for 40 weeks post-treatment. The 4 week CQR for varenicline and placebo was 47.3% and 14.3%, respectively and the CA week 9-52 was 19.8% (varenicline) vs. 7.4% (placebo).

Deaths and serious cardiovascular events were adjudicated by a blinded, committee. The following adjudicated events occurred with a frequency ≥ 1% in either treatment group during treatment (or in the 30-day period after treatment): nonfatal myocardial infarction (1.1% vs. 0.3% for CHAMPIX and placebo, respectively), and hospitalisation for angina pectoris (0.6% vs. 1.1%). During non-treatment follow up to 52 weeks, the adjudicated events included need for coronary revascularisation (2.0% vs. 0.6%), hospitalisation 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 revascularisation underwent the procedure as part of management of nonfatal MI and hospitalisation for angina. Cardiovascular death occurred in 0.3% of patients in the CHAMPIX arm and 0.6% of patients in the placebo arm over the course of the 52-week study.

A meta-analysis of 15 clinical trials of ≥ 12 weeks treatment duration, including 7002 patients (4190 CHAMPIX, 2812 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.

The key cardiovascular safety analysis included occurrence and timing of a composite endpoint of Major Adverse Cardiovascular Events (MACE), defined as cardiovascular death, nonfatal MI, and nonfatal stroke. These events included in the endpoint were adjudicated by a blinded, independent committee. Overall, a small number of MACE occurred during treatment in the trials included in the meta-analysis (CHAMPIX 7 [0.17%]; placebo 2 [0.07%]). Additionally, a small number of MACE occurred up to 30 days after treatment (CHAMPIX 13 [0.31%]; placebo 6 [0.21%]).

The meta-analysis showed that exposure to CHAMPIX resulted in a hazard ratio for MACE of 2.83 (95% confidence interval from 0.76 to 10.55, p=0.12) for patients during treatment and 1.95 (95% confidence interval from 0.79 to 4.82, p=0.15) for patients up to 30 days after treatment. These are equivalent to an estimated increase of 6.5 MACE events and 6.3 MACE events per 1,000 patient-years, respectively of exposure. The hazard ratio for MACE was higher in patients with cardiovascular risk factors in addition to smoking compared with that in patients without cardiovascular risk factors other than smoking. There were similar rates of all-cause mortality (CHAMPIX 6 [0.14%]; placebo 7 [0.25%]) and cardiovascular mortality (CHAMPIX 2 [0.05%]; placebo 2 [0.07%]) in the CHAMPIX arms compared with the placebo arms in the meta-analysis.

Cardiovascular safety assessment study in subjects with and without a history of psychiatric disorder
The cardiovascular (CV) safety of CHAMPIX was evaluated in the Study in Subjects with and without a History of Psychiatric Disorder (parent study; see section 5.1 - *Neuropsychiatric safety*) and its non-treatment extension, the Cardiovascular Safety Assessment Study, which enrolled 4595 of the 6293 subjects who completed the parent study (N=8058) and followed them through week 52. Of all subjects treated in the parent study, 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 events (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.

	CHAMPIX 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)	

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.

Subjects with mild-moderate chronic obstructive pulmonary disease (COPD)
The efficacy and safety of CHAMPIX (1 mg twice daily) for smoking cessation in subjects with mild-moderate COPD was demonstrated in a randomised double-blind placebo-controlled clinical trial. In this 52-week duration study, patients received treatment for 12 weeks, followed by a 40-week non-treatment follow-up phase. The primary endpoint of the study was the CO-confirmed, 4-week Continuous Quit Rate (4W CQR) from week 9 through week 12 and a key secondary endpoint was the Continuous Abstinence (CA) from Week 9 through Week 52. The safety profile of varenicline was comparable to what was reported in other trials in the general population, including pulmonary safety. The results for the 4W CQR (weeks 9 through 12) and CA rate (weeks 9 through 52) are shown in the following table:

	4W CQR	CA Wk 9-52
CHAMPIX, (n = 248)	42.3%	18.5%
Placebo, (n = 251)	8.8%	5.6%
Odds ratio (CHAMPIX vs. Placebo)	8.40 $p < 0.0001$	4.04 $p < 0.0001$

Study in subjects with a history of major depressive disorder
The efficacy of varenicline was confirmed in a randomised placebo-controlled trial in 525 subjects with a history of major depression in the past two years or under current stable treatment. The cessation rates in this population were similar to those reported in the general population. Continuous abstinence rate between weeks 9-12 was 35.9% in the varenicline treatment group versus 15.6% in the placebo group (OR 3.35 (95% CI 2.16-5.21)) and between weeks 9-52 was 20.3% versus 10.4% respectively (OR 2.36 (95% CI 1.40-3.98)). 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%). Psychiatric scales showed no differences between the varenicline and placebo groups and no overall worsening of depression, or other psychiatric symptoms, during the study in either treatment group.

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, randomised 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 behaviour prior to enrolment (lifetime history) and after the end of active treatment period (on Days 33 to 85 after the last dose of treatment). 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. Although 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 are not sufficient to allow for definitive conclusions to be drawn about the safety in patients with schizophrenia or schizoaffective disorder.

Neuropsychiatric Safety Study in Subjects with and without a History of Psychiatric Disorder:
Varenicline was evaluated in a randomised, 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 randomised 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/or moderate or severe events of agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal ideation, suicidal behaviour or completed suicide.

The following table shows the rates of the composite NPS adverse event primary endpoint by treatment group and the risk differences (RDs) (95% CI) vs placebo in the **non-psychiatric cohort**.

In addition, the table shows the subset of the composite NPS AE endpoint 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)	
Composite NPS AE Endpoint of severe intensity n (%)	1 (0.1)	4 (0.4)	3 (0.3)	5 (0.5)

AE, adverse event; NRT=Nicotine replacement therapy patch

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. The use of varenicline, bupropion and NRT in the non-psychiatric cohort was not associated with a significantly increased risk of NPS adverse events in the composite primary endpoint compared with placebo (95% CIs were lower than or included zero).

The percentage of subjects with suicidal ideation and/or behaviour 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 behaviour and/or ideation	7 (0.7)	4 (0.4)	3 (0.3)	7 (0.7)
Suicidal behaviour	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 behaviour and/or ideation	3 (0.4)	2 (0.2)	3 (0.4)	4 (0.5)
Suicidal behaviour	0	1 (0.1)	0	0
Suicidal ideation	3 (0.4)	2 (0.2)	3 (0.4)	4 (0.5)

NRT=Nicotine replacement therapy patch

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 endpoint by treatment group and the 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 composite NPS AE endpoint 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)	
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 behaviour[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)

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, and the incidence of events in the composite endpoint was higher for each of the active treatments compared to placebo. However, the use of varenicline, bupropion and NRT in the psychiatric cohort was not associated with a significantly increased risk of NPS adverse events in the composite primary endpoint compared with placebo (95% CIs included zero).

In the psychiatric cohort, the percentage of subjects with suicidal ideation and/or behaviour 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 behaviour and/or ideation	27 (2.7)	15 (1.5)	20 (2.0)	25 (2.5)
Suicidal behaviour	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 behaviour and/or ideation	14 (1.7)	4 (0.5)	9 (1.1)	11 (1.4)
Suicidal behaviour	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.

In both cohorts, subjects treated with varenicline demonstrated statistical superiority of CO-confirmed abstinence during weeks 9 through 12 and 9 through 24 compared to subjects treated with bupropion, nicotine patch and placebo (please see table below).

The key efficacy results are summarised in the following table:

	Non-psychiatric Cohort	Psychiatric Cohort
CA 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
CA 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

CA = 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.

Treatment discontinuation
The treatment discontinuation rate due to adverse reactions was 11.4% for varenicline compared with 9.7% for placebo. In this group, the discontinuation rates for the most common adverse reactions 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).

Analyses of Clinical Trials:

A meta-analysis of 5 randomised, double-blind, placebo controlled trials, including 1907 patients (1130 varenicline, 777 placebo), was conducted to assess suicidal ideation and behaviour 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 behaviour in patients treated with varenicline compared to patients treated with placebo, as shown in the table below. Of the 55 patients who reported suicidal ideation or behaviour, 48 (24 varenicline, 24 placebo) were from the two trials that enrolled patients with a history of schizophrenia/ schizoaffective disorder, or of 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 Behaviour 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 behaviour* [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 behaviour

** 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, randomised, 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: 0.89-1.15). 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 hospitalisations 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).

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* as compared to infants born to mothers who smoked during pregnancy had lower rates of congenital malformations (3.6% vs 4.3%), stillbirth (0.3% vs 0.5%), preterm birth (7.5% vs 7.9%), small for gestational age (12.5% vs 17.1%), and premature rupture of membrane (3.6% vs 5.4%).

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 litres (%CV= 50) at steady-state. Plasma protein binding of varenicline is low (≤ 20%) and independent of both age and renal function. In rodents, varenicline is transferred through the placenta and excreted in milk.

Biotransformation

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.

In vitro studies demonstrate that varenicline does not inhibit cytochrome P450 enzymes (IC50 > 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.

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 via the organic cationic transporter, OCT2 (see section 4.5).

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 medicinal products, as demonstrated in specific pharmacokinetic studies and in population pharmacokinetic analyses.

Hepatic impairment
Due to the absence of significant hepatic metabolism, varenicline pharmacokinetics should be unaffected in patients with hepatic impairment. (see section 4.2).

Renal impairment
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 haemodialysis (see section 4.2).

Elderly
The pharmacokinetics of varenicline in elderly patients with normal renal function (aged 65-75 years) is similar to that of younger adult subjects (see section 4.2). For elderly patients with reduced renal function please refer to section 4.2.

Paediatric population
Single and multiple-dose pharmacokinetics of varenicline have been investigated in paediatric 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 twice daily was given, steady-state daily exposure of varenicline was, on average, higher (by approximately 40%) in adolescent patients with bodyweight ≤ 55 kg compared to that noted in the adult population. Efficacy and safety has not been demonstrated in the paediatric population below 18 years of age and no recommendation on a posology can be made (see section 4.2).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, fertility and embryo-foetal development. In male rats dosed for 2 years with varenicline, there was a dose-related increase in the incidence of hibernoma (tumour of the brown fat). In the offspring of pregnant rats treated with varenicline there were decreases in fertility and increases in the auditory startle response (see section 4.6). These effects were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use. Nonclinical data indicate varenicline has reinforcing properties albeit with lower potency than nicotine. In clinical studies in humans, varenicline showed low abuse potential.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablets' core

0.5 mg and 1 mg Tablets
Cellulose, Microcrystalline
Calcium Hydrogen Phosphate Anhydrous
Croscarmellose Sodium
Silica, Colloidal Anhydrous
Magnesium Stearate

Film coating

0.5 mg Tablet
Hypromellose
Titanium Dioxide (E171)
Macrogol 400
Triacetin

1 mg Tablet

Hypromellose
Titanium Dioxide (E171)
Indigo Carmine Aluminium Lake E132
Macrogol 400
Triacetin

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Blisters: 3 years

6.4 Special precautions for storage

Store below 30°C

6.5 Nature and contents of container

Treatment initiation packs

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

PCTFE/PVC blisters with aluminium foil backing containing one clear blister of 11 x 0.5 mg film-coated tablets and a second clear blister containing 14 x 1 mg film-coated tablets in a carton.

PCTFE/PVC blisters with aluminium foil backing containing one clear blister of 11 x 0.5 mg and 14 x 1 mg film-coated tablets and a second clear blister of 28 x 1 mg film-coated tablets in secondary heat sealed card packaging.

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

PVC blisters with aluminium foil backing containing one clear blister of 11 x 0.5 mg film-coated tablets and a second clear blister containing 14 x 1 mg film-coated tablets in a carton.

PVC blisters with aluminium foil backing containing one clear blister of 11 x 0.5 mg and 14 x 1 mg film-coated tablets and a second clear blister of 28 x 1 mg film-coated tablets in secondary heat sealed card packaging.

One outer carton containing:

PCTFE/PVC blisters with aluminium foil backing containing one clear blister of 11 x 0.5 mg and 14 x 1 mg film-coated tablets and a second clear blister of 28 x 1 mg film-coated tablets in one secondary heat sealed card pack and PCTFE/PVC blisters with aluminium foil backing in two secondary heat sealed card packs each containing 56 x 1 mg film-coated tablets.

One outer carton containing:

PVC blisters with aluminium foil backing containing one clear blister of 11 x 0.5 mg and 14 x 1 mg film-coated tablets and a second clear blister of 28 x 1 mg film-coated tablets in one secondary heat sealed card pack and PVC blisters with aluminium foil backing in two secondary heat sealed card packs each containing 56 x 1 mg film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent
CT13 9NJ
UK

8. MARKETING AUTHORISATION NUMBER(S)

Treatment initiation packs:

EU/1/06/360/003
EU/1/06/360/008
EU/1/06/360/012
EU/1/06/360/014
EU/1/06/360/019
EU/1/06/360/023
EU/1/06/360/025
EU/1/06/360/026

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 September 2006
Date of latest renewal: 29 June 2016

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency http://www.ema.europa.eu/

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

R-Pharm Germany GmbH
Heinrich-Mack-Str. 35, 89257 Illertissen
Germany

Pfizer Italia S.r.l.
Località Marino del Tronto, 63100
Ascoli Piceno (AP)
Italy

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
  Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Obligation to conduct post-authorisation measures**

Not Applicable.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Maintenance pack
Heat sealed card pack containing either 2 blister packs of 14 x 0.5 mg varenicline film-coated tablets or 2 blister packs of 28 x 0.5 mg varenicline film-coated tablets– inner and outer labelling

1. NAME OF THE MEDICINAL PRODUCT

CHAMPIX 0.5 mg
Film-coated tablets
Varenicline

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 0.5 mg varenicline (as tartrate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Maintenance pack containing
28 film-coated tablets
56 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use
numbers 1 to 14
numbers 1 to 28
sun as symbol
moon as symbol

Do not use if box has been opened.

Keep the package intact

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: MM/YYYY

9. SPECIAL STORAGE CONDITIONS

Store below 30°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent
CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/360/006
EU/1/06/360/007
EU/1/06/360/017
EU/1/06/360/018

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

CHAMPIX 0.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister Pack of 14 x 0.5 mg and 28 x 0.5 mg varenicline film-coated tablets, Heat Sealed Card

1. NAME OF THE MEDICINAL PRODUCT

CHAMPIX 0.5 mg
Varenicline

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Ltd (as MA Holder Logo)

3. EXPIRY DATE

EXP: MM/YYYY

4. BATCH NUMBER

Lot:

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Maintenance pack
Heat sealed card pack containing either 2 blister packs of 14 x 1 mg varenicline film-coated tablets or 2 blister packs of 28 x 1 mg varenicline film-coated tablets– inner and outer labelling

1. NAME OF THE MEDICINAL PRODUCT

CHAMPIX 1 mg
Film-coated tablets
Varenicline

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 1 mg varenicline (as tartrate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Maintenance pack containing
28 film-coated tablets
56 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use
numbers 1 to 14
numbers 1 to 28
sun as symbol
moon as symbol

Do not use if box has been opened.

Keep the package intact

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: MM/YYYY

9. SPECIAL STORAGE CONDITIONS

Store below 30°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent
CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/360/004
EU/1/06/360/005
EU/1/06/360/015
EU/1/06/360/016

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

CHAMPIX 1 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister Pack of 14 x 1 mg and 28 x 1 mg varenicline film-coated tablets, Heat Sealed Card

1. NAME OF THE MEDICINAL PRODUCT

CHAMPIX 1 mg
Varenicline

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Ltd (as MA Holder Logo)

3. EXPIRY DATE

EXP: MM/YYYY

4. BATCH NUMBER

Lot:

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Maintenance pack
Carton Pack containing 2 blister packs of 14 x 1 mg varenicline film-coated tablets or 4 blister packs of 14 x 1 mg varenicline film-coated tablets or 8 blister packs of 14 x 1 mg varenicline film-coated tablets or 10 blister packs of 14 x 1 mg varenicline film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

CHAMPIX 1 mg
Film-coated tablets
Varenicline

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 1 mg varenicline (as tartrate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

28 Film-coated tablets
56 Film-coated tablets
112 Film-coated tablets
140 Film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

Do not use if box has been opened.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: MM/YYYY

9. SPECIAL STORAGE CONDITIONS

Store below 30°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent
CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/360/009
EU/1/06/360/010
EU/1/06/360/011
EU/1/06/360/013
EU/1/06/360/020
EU/1/06/360/021
EU/1/06/360/022
EU/1/06/360/024

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

CHAMPIX 1 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister Pack of 14 x 1 mg varenicline film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

CHAMPIX 1 mg
Varenicline

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Ltd (as MA Holder Logo)

3. EXPIRY DATE

EXP: MM/YYYY

4. BATCH NUMBER

Lot:

5. OTHER

sun as symbol
moon as symbol

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

2-week treatment initiation pack
Heat sealed card pack containing 1 blister pack of 11 x 0.5 mg varenicline film-coated tablets and 1 blister pack of 14 x 1 mg varenicline film-coated tablets – inner and outer labelling

1. NAME OF THE MEDICINAL PRODUCT

CHAMPIX 0.5 mg
CHAMPIX 1 mg
Film-coated tablets
Varenicline

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 0.5 mg or 1 mg varenicline (as tartrate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Initiation pack containing
Film-coated tablets
11 x 0.5 mg and 14 x 1 mg

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

Start at day 1
The day you stop smoking should usually be between day 8 and day 14.
To quit gradually, please refer to package leaflet for dosing instructions.

Week 1
Week 2

Numbers 1 to 14
sun as symbol
moon as symbol

Do not use if box has been opened.

Keep the package intact
Does not contain a tablet

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: MM/YYYY

9. SPECIAL STORAGE CONDITIONS

Store below 30°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent
CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/360/003
EU/1/06/360/014

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

CHAMPIX
0.5 mg
1 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister Pack of 11 x 0.5 mg varenicline film-coated tablets, Heat Sealed Card

1. NAME OF THE MEDICINAL PRODUCT

CHAMPIX 0.5 mg
Varenicline

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Ltd (as MA Holder Logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister Pack of 14 x 1 mg varenicline film-coated tablets, Heat Sealed Card

1. NAME OF THE MEDICINAL PRODUCT

CHAMPIX 1 mg
Varenicline

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Ltd (as MA Holder Logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Treatment initiation pack
Carton pack with 1 blister pack of 11 x 0.5 mg varenicline film-coated tablets and 1 blister pack of 14 x 1 mg varenicline film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

CHAMPIX 0.5 mg
CHAMPIX 1 mg
Film-coated tablets
Varenicline

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 0.5 mg or 1 mg varenicline (as tartrate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets
11 x 0.5 mg and 14 x 1 mg

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

Do not use if box has been opened.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: MM/YYYY

9. SPECIAL STORAGE CONDITIONS

Store below 30°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent
CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/360/008
EU/1/06/360/019

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

CHAMPIX
0.5 mg
1 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister Pack of 11 x 0.5 mg varenicline film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

CHAMPIX 0.5 mg
Varenicline

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Ltd (as MA Holder Logo)

3. EXPIRY DATE

EXP: MM/YYYY

4. BATCH NUMBER

Lot:

5. OTHER

sun as symbol
moon as symbol

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister Pack of 14 x 1 mg varenicline film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

CHAMPIX 1 mg
Varenicline

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Ltd (as MA Holder Logo)

3. EXPIRY DATE

EXP: MM/YYYY

4. BATCH NUMBER

Lot:

5. OTHER

sun as symbol
moon as symbol

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

4-week treatment initiation pack
Heat sealed card pack containing 1 blister pack of 11 x 0.5 mg and 14 x 1 mg varenicline film-coated tablets and 1 blister pack of 28 x 1 mg varenicline film-coated tablets – inner and outer labelling

1. NAME OF THE MEDICINAL PRODUCT

CHAMPIX 0.5 mg
CHAMPIX 1 mg
Film-coated tablets
Varenicline

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 0.5 mg or 1 mg varenicline (as tartrate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

4-week treatment initiation pack containing:
11 x 0.5 mg film-coated tablets
and
42 x 1 mg film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

Start at Day 1
The day you stop smoking should usually be between day 8 and day 14.
To quit gradually, please refer to package leaflet for dosing instructions.

Week 1
Week 2-4

Numbers 1 to 28
sun as symbol
moon as symbol

Do not use if box has been opened.

Keep the package intact
Does not contain any tablets

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: MM/YYYY

9. SPECIAL STORAGE CONDITIONS

Store below 30°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent
CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/360/012
EU/1/06/360/023

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

CHAMPIX
0.5 mg
1 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister Pack of 11 x 0.5 mg and 14 x 1 mg varenicline film-coated tablets, Heat Sealed Card

1. NAME OF THE MEDICINAL PRODUCT

CHAMPIX 0.5 mg
CHAMPIX 1 mg
Varenicline

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Ltd (as MA Holder Logo)

3. EXPIRY DATE

EXP: MM/YYYY

4. BATCH NUMBER

Lot:

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister Pack of 28 x 1 mg varenicline film-coated tablets, Heat Sealed Card

1. NAME OF THE MEDICINAL PRODUCT

CHAMPIX 1 mg
Varenicline

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Ltd (as MA Holder Logo)

3. EXPIRY DATE

EXP: MM/YYYY

4. BATCH NUMBER

Lot:

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

12-week Treatment Initiation Pack
One Outer Carton Pack containing:
1 x heat sealed card pack containing 11 x 0.5 mg and 14 x 1 mg varenicline film-coated tablets and 1 blister pack of 28 x 1 mg varenicline film-coated tablets and 2 x heat sealed card packs each containing 2 blister packs of 28 x 1 mg varenicline film-coated tablets – outer and inner labelling.

Contains Blue Box

1. NAME OF THE MEDICINAL PRODUCT

CHAMPIX 0.5 mg
CHAMPIX 1 mg
Film-coated tablets
Varenicline

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 0.5 mg or 1 mg varenicline (as tartrate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

12-week Treatment Initiation Pack
containing:
11 x 0.5 mg film-coated tablets
and
154 x 1 mg film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

Start at Day 1
The day you stop smoking should usually be between day 8 and day 14.
To quit gradually, please refer to package leaflet for dosing instructions.

Do not use if box has been opened.

Keep the package intact

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: MM/YYYY

9. SPECIAL STORAGE CONDITIONS

Store below 30°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent
CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/360/025
EU/1/06/360/026

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

CHAMPIX
0.5 mg
1 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON
4-week treatment initiation pack
Heat sealed card pack containing 1 blister pack of 11 x 0.5 mg and 14 x 1 mg varenicline film-coated tablets and 1 blister pack of 28 x 1 mg varenicline film-coated tablets – inner and outer labelling.

Contains No Blue Box

1. NAME OF THE MEDICINAL PRODUCT

CHAMPIX 0.5 mg
CHAMPIX 1 mg
Film-coated tablets
Varenicline

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 0.5 mg or 1 mg varenicline (as tartrate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

4-week treatment initiation pack containing:
11 x 0.5 mg film-coated tablets
and
42 x 1 mg film-coated tablets

Can’t be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

Start at Day 1
The day you stop smoking should usually be between day 8 and day 14.
To quit gradually, please refer to package leaflet for dosing instructions.

Week 1
Week 2-4

Numbers 1 to 28
sun as symbol
moon as symbol

Do not use if box has been opened.

Keep the package intact

Does not contain any tablets

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: MM/YYYY

9. SPECIAL STORAGE CONDITIONS

Store below 30°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent
CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/360/025
EU/1/06/360/026

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

CHAMPIX
0.5 mg
1 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

Not Applicable

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

Not Applicable

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister Pack of 11 x 0.5 mg and 14 x 1 mg varenicline film-coated tablets, Heat Sealed Card

1. NAME OF THE MEDICINAL PRODUCT

CHAMPIX 0.5 mg
CHAMPIX 1 mg
Varenicline

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Ltd (as MA Holder Logo)

3. EXPIRY DATE

EXP: MM/YYYY

4. BATCH NUMBER

Lot:

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister Pack of 28 x 1 mg varenicline film-coated tablets, Heat Sealed Card

1. NAME OF THE MEDICINAL PRODUCT

CHAMPIX 1 mg
Varenicline

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Ltd (as MA Holder Logo)

3. EXPIRY DATE

EXP: MM/YYYY

4. BATCH NUMBER

Lot:

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON
Maintenance pack
Heat sealed card pack containing 2 blister packs of 28 x 1 mg varenicline film-coated tablets– inner and outer labelling

Contains No Blue Box

1. NAME OF THE MEDICINAL PRODUCT

CHAMPIX 1 mg
Film-coated tablets
Varenicline

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 1 mg varenicline (as tartrate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Maintenance pack containing
56 film-coated tablets

Can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.
numbers 1 to 14
numbers 1 to 28
sun as symbol
moon as symbol

Do not use if box has been opened.

Keep the package intact

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: MM/YYYY

9. SPECIAL STORAGE CONDITIONS

Store below 30°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent
CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/360/025
EU/1/06/360/026

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

CHAMPIX 1 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

Not Applicable

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

Not Applicable

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister Pack of 28 x 1 mg varenicline film-coated tablets, Heat Sealed Card

1. NAME OF THE MEDICINAL PRODUCT

CHAMPIX 1 mg
Varenicline

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Ltd (as MA Holder Logo)

3. EXPIRY DATE

EXP: MM/YYYY

4. BATCH NUMBER

Lot:

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

High-density polyethylene (HDPE) bottle packaging for 56 x 0.5 mg varenicline film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

CHAMPIX 0.5 mg
Film-coated tablets
Varenicline

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 0.5 mg varenicline (as tartrate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

56 Film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: MM/YYYY

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent
CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/360/001

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

CHAMPIX 0.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE THE IMMEDIATE PACKAGING

High-density polyethylene (HDPE) bottle label for 56 x 0.5 mg varenicline film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

CHAMPIX 0.5 mg
Film-coated tablets
Varenicline

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 0.5 mg varenicline (as tartrate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

56 Film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: MM/YYYY

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Ltd (as MA Holder Logo)

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/360/001

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

Not Applicable

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

Not Applicable

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

High-density polyethylene (HDPE) bottle packaging for 56 x 1 mg varenicline film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

CHAMPIX 1 mg
Film-coated tablets
Varenicline

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 1 mg varenicline (as tartrate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

56 Film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: MM/YYYY

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent
CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/360/002

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

CHAMPIX 1 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE THE IMMEDIATE PACKAGING

High-density polyethylene (HDPE) bottle label for 56 x 1 mg varenicline film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

CHAMPIX 1 mg
Film-coated tablets
Varenicline

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 1 mg varenicline (as tartrate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

56 Film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: MM/YYYY

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Ltd (as MA Holder Logo)

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/360/002

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

Not Applicable

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

Not Applicable

B. PACKAGE LEAFLET

Package leaflet: Information for the user

CHAMPIX 0.5 mg film-coated tablets
CHAMPIX 1 mg film-coated tablets
Varenicline

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What CHAMPIX is and what it is used for

CHAMPIX contains the active substance varenicline. CHAMPIX is a medicine which is used in adults to help them stop smoking.

CHAMPIX can help to relieve the craving and withdrawal symptoms associated with stopping smoking.

CHAMPIX can also reduce the enjoyment of cigarettes if you do smoke when on treatment.

2. What you need to know before you take CHAMPIX

Do not take CHAMPIX:

- If you are allergic to varenicline or any of the other ingredients of this medicine (listed in section 6)

Warnings and precautions
Talk to your doctor or pharmacist before taking CHAMPIX.

There have been reports of depression, suicidal ideation and behaviour and suicide attempts in patients taking CHAMPIX. If you are taking CHAMPIX and develop agitation, depressed mood, changes in behaviour that are of concern to you or your family or if you develop suicidal thoughts or behaviours you should stop taking CHAMPIX and contact your doctor immediately for treatment assessment.

The effects of stopping smoking
The effects of changes in your body resulting from stopping smoking, with or without treatment with CHAMPIX, may alter the way other medicines work. Therefore, in some cases an adjustment of the dose may be necessary. See below under 'Other medicines and CHAMPIX' for further details.

For some people, stopping smoking with or without treatment has been associated with an increased risk of experiencing changes in thinking or behaviour, feelings of depression and anxiety and can be associated with a worsening of psychiatric disorder. If you have a history of psychiatric disorder you should discuss this with your doctor.

Heart symptoms
New or worse heart or blood vessel (cardiovascular) problems have been reported primarily 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 symptoms of a heart attack or stroke.

Seizures
Tell your doctor if you have experienced seizures or have epilepsy before your start CHAMPIX treatment. Some people have reported seizures while taking CHAMPIX.

Hypersensitivity reactions
Stop taking CHAMPIX and tell your doctor immediately if you experience any of the following signs and symptoms that may indicate a serious allergic reaction: swelling of the face, lips, tongue, gums, throat or body and/or difficulty breathing, wheezing.

Skin reactions
Potentially life-threatening skin rashes (Stevens-Johnson syndrome and Erythema Multiforme) have been reported with the use of CHAMPIX. If you develop a rash or if your skin starts to peel or blister you should stop taking CHAMPIX and seek emergency medical help.

Children and adolescents
CHAMPIX is not recommended for use in children or adolescents below 18 years as safety and efficacy have not yet been established.

Other medicines and CHAMPIX
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

In some cases as a result of stopping smoking, with or without CHAMPIX, an adjustment of the dose of other medicines may be necessary. Examples include theophylline (a medicine to treat breathing problems), warfarin (a medicine to reduce blood clotting), and insulin (a medicine to treat diabetes). If in doubt, you should consult your doctor or pharmacist.

If you have severe kidney disease you should avoid taking cimetidine (a medicine used for gastric problems) at the same time as CHAMPIX as this may cause increased blood levels of CHAMPIX.

Use of CHAMPIX with other therapies for smoking cessation
Consult your doctor before using CHAMPIX in combination with other smoking cessation therapies.

CHAMPIX with food and drink
There have been some reports of increased intoxicating effects of alcohol in patients taking CHAMPIX. However, it is not known if CHAMPIX actually increases alcohol intoxication.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

It is preferable to avoid the use of CHAMPIX while you are pregnant. Talk to your doctor if you are intending to become pregnant.

Although it was not studied, CHAMPIX may pass into breast milk. You should ask your doctor or pharmacist for advice before taking CHAMPIX.

Driving and using machines
CHAMPIX may produce dizziness and sleepiness. You should not drive, operate complex machinery or engage in any other potentially hazardous activities until you know whether this medicine affects your ability to perform these activities.

3. How to take CHAMPIX

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

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

Before starting your course of CHAMPIX you should usually decide on a date in the second week of treatment (between day 8 and day 14) when you will stop smoking. If you are not willing or able to set a target quit date within 2 weeks, you may choose your own target quit date within 5 weeks after starting treatment. You should write this date on the pack as a reminder.

CHAMPIX comes as a white tablet (0.5 mg) and a light blue tablet (1 mg). You start with the white tablet and then usually go to the light blue tablet. See the chart below for the usual dosing instructions which you should follow from Day 1.

Week 1	**Dose**
Day 1 - 3	From day 1 to day 3, you should take one white CHAMPIX 0.5 mg film-coated tablet once a day.
Day 4 - 7	From day 4 to day 7, you should take one white CHAMPIX 0.5 mg film-coated tablet twice daily, once in the morning and once in the evening, at about the same time each day.

Week 2	
Day 8 – 14	From day 8 to day 14, you should take one light blue CHAMPIX 1 mg film-coated tablet twice daily, once in the morning and once in the evening, at about the same time each day.

Weeks 3 - 12	
Day 15 - end of treatment	From day 15 until the end of treatment, you should take one light blue CHAMPIX 1 mg film-coated tablet twice daily, once in the morning and once in the evening, at about the same time each day.

After 12 weeks of treatment, if you have stopped smoking, your doctor may recommend an additional 12 weeks of treatment with CHAMPIX 1 mg film-coated tablets twice daily to help avoid returning back to smoking.

If you are not able or willing to quit smoking straight away, you should reduce smoking during the first 12 weeks of treatment and quit by the end of that treatment period. You should then continue to

take CHAMPIX 1 mg film-coated tablets twice daily for a further 12 weeks resulting in a total of 24 weeks of treatment.

Should you experience adverse effects that you cannot tolerate your doctor may decide to reduce your dose temporarily or permanently to 0.5 mg twice daily.

If you have problems with your kidneys, you should speak to your doctor before taking CHAMPIX. You may need a lower dose.

Champix is for oral use.
The tablets should be swallowed whole with water and can be taken with or without food.

If you take more CHAMPIX than you should
If you accidentally take more CHAMPIX than your doctor prescribed, you must seek medical advice or go to the nearest hospital casualty department immediately. Take your box of tablets with you.

If you forget to take CHAMPIX
Do not take a double dose to make up for a forgotten tablet. It is important that you take CHAMPIX regularly at the same time each day. If you forget to take a dose, take it as soon as you remember. If, it is within 3-4 hours before your next dose, do not take the tablet that you have missed.

If you stop taking CHAMPIX
It has been shown in clinical trials that taking all doses of your medicine at the appropriate times and for the recommended duration of treatment described above will increase your chances of stopping smoking. Therefore, unless your doctor instructs you to stop treatment, it is important to keep taking CHAMPIX, according to the instructions described in the table above.

In smoking cessation therapy, risk of returning to smoking may be elevated in the period immediately following the end of treatment. You may temporarily experience increased irritability, urge to smoke, depression and/or sleep disturbances when you stop taking CHAMPIX. Your doctor may decide to gradually lower your dose of CHAMPIX at the end of treatment.

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

4. Possible side effects

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

Giving up smoking with or without treatment can cause various symptoms. These could include changes of mood (like feeling depressed, irritable, frustrated or anxious), sleeplessness, difficulty concentrating, decreased heart rate and increased appetite or weight gain.

You should be aware of the possible emergence of serious neuropsychiatric symptoms, such as agitation, depressed mood, or changes in behaviour during a quit attempt with or without CHAMPIX and you should contact a doctor or pharmacist if you experience such symptoms.

Serious side effects of either an uncommon or rare frequency have occurred in people attempting to quit smoking with CHAMPIX: seizure, stroke, heart attack, suicidal thoughts, loss of contact with reality and unable to think or judge clearly (psychosis), changes in thinking or behaviour (such as aggression and abnormal behaviour). There have also been reports of severe skin reactions including Erythema Multiforme (a type of rash) and Stevens-Johnson Syndrome (a serious illness with blistering of the skin, mouth, around the eyes or genitals) and serious allergic reactions including angioedema (swelling of the face, mouth, or throat).

- Very common: may affect more than 1 in 10 people

    - Inflammation of the nose and throat, abnormal dreams, difficulty sleeping, headache,
    - Nausea

- Common: may affect up to 1 in 10 people

    - Chest infection, inflammation of the sinuses
    - Increased weight, decreased appetite, increased appetite
    - Sleepiness, dizziness, changes in the way things taste
    - Shortness of breath, cough
    - Heartburn, vomiting, constipation, diarrhoea, feeling bloated, abdominal pain, toothache, indigestion, flatulence, dry mouth
    - Skin rash, itching
    - Joint ache, muscle ache, back pain
    - Chest pain, tiredness

- Uncommon: may affect up to 1 in 100 people

    - Fungal infection, viral infection
    - Feeling of panic, difficulty thinking, restlessness, mood swings, depression, anxiety, hallucinations, changes in sex drive
    - Seizure, tremor, feeling sluggish, less sensitive to touch
    - Conjunctivitis, eye pain
    - Ringing in the ears
    - Angina, rapid heart rate, palpitations, increased heart rate
    - Increased blood pressure, hot flush
    - Inflammation of nose, sinuses and throat, congestion of nose, throat and chest, hoarseness, hay fever, throat irritation, congested sinuses, excess mucous from nose causing cough, runny nose
    - Red blood in stools, irritated stomach, change of bowel habit, belching, mouth ulcers, pain in the gums
    - Reddening of the skin, acne, increased sweating, night sweats
    - Muscle spasms, chest wall pain
    - Abnormally frequent urination, urination at night
    - Increased menstrual flow
    - Chest discomfort, flu like illness, fever, feeling weak or unwell
    - High blood sugar
    - Heart attack
    - Suicidal thoughts
    - Changes in thinking or behaviour (such as aggression)

- Rare: may affect up to 1 in 1,000 people

    - Excessive thirst
    - Feeling unwell or unhappy, slow thinking
    - Stroke
    - Increased muscle tension, difficulty with speech, difficulty with coordination, reduced sense of taste, altered sleep pattern
    - Disturbed vision, eyeball discolouration, dilated pupils, sensitivity to light, shortsightedness, watery eyes
    - Irregular heart beat or heart rhythm disturbances
    - Throat pain, snoring
    - Blood in vomit, abnormal stools, coated tongue
    - Stiff joints, rib pain
    - Glucose in urine, increased urine volume and frequency

- Vaginal discharge, changes in sexual ability
- Feeling cold, cyst
- Diabetes
- Sleep walking
- Loss of contact with reality and unable to think or judge clearly (psychosis)
- Abnormal behaviour
- Severe skin reactions including Erythema Multiforme (a type of rash) and Stevens-Johnson Syndrome (a serious illness with blistering of the skin, mouth, around the eyes or genitals)
- Serious allergic reactions including angioedema (swelling of the face, mouth, or throat)

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store CHAMPIX

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the card packaging or carton after EXP. The expiry date refers to the last day of that month.

Blisters: Store below 30°C
Bottle: This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What CHAMPIX contains
- The active substance is varenicline.
- Each 0.5 mg film-coated tablet contains 0.5 mg of varenicline (as tartrate).
- Each 1 mg film-coated tablet contains 1 mg of varenicline (as tartrate).
- The other ingredients are:

Tablet Core - CHAMPIX 0.5 mg and 1 mg film-coated tablets
Cellulose, Microcrystalline Calcium Hydrogen Phosphate Anhydrous Croscarmellose Sodium Silica, Colloidal Anhydrous Magnesium Stearate

Tablet film coating - CHAMPIX 0.5 mg film-coated tablets
Hypromellose Titanium dioxide (E171) Macrogol 400 Triacetin

Tablet film coating - CHAMPIX 1 mg film-coated tablets
Hypromellose Titanium dioxide (E171) Macrogol 400 Indigo Carmine Aluminium Lake (E132) Triacetin

What CHAMPIX looks like and contents of the pack

- CHAMPIX 0.5 mg film-coated tablets are white, film-coated, modified capsular shaped tablets, marked "*Pfizer*" and "CHX 0.5"

- CHAMPIX 1 mg film-coated tablets are light blue film-coated, modified capsular shaped tablets, marked "*Pfizer*" and "CHX 1.0"

CHAMPIX is available in the following pack presentations:

- A treatment initiation pack containing 2 blisters; 1 clear blister of 11 x CHAMPIX 0.5 mg film-coated tablets and 1 clear blister of 14 x CHAMPIX 1 mg film-coated tablets in card packaging.
- A treatment initiation pack containing 2 blisters; 1 clear blister of 11 x CHAMPIX 0.5 mg and 14 x 1 mg film-coated tablets and 1 clear blister of 28 x CHAMPIX 1 mg film-coated tablets in card packaging.
- A treatment initiation pack in an outer carton containing one pack with 1 clear blister of 11 x CHAMPIX 0.5 mg and 14 x 1 mg film-coated tablets and 1 clear blister of 28 x CHAMPIX 1 mg film-coated tablets in card packaging and two packs each containing 2 clear blisters of 28 x CHAMPIX 1 mg film-coated tablets in card packaging.
- A follow-on (maintenance) pack containing 2 clear blisters of 14 x CHAMPIX 1 mg film-coated tablets in card packaging.
- A follow-on (maintenance) pack containing 2 clear blisters of 28 x CHAMPIX 1 mg film-coated tablets in card packaging.
- A follow-on (maintenance) pack containing 2 clear blisters of 14 x CHAMPIX 0.5 mg film-coated tablets in card packaging.
- A follow-on (maintenance) pack containing 2 clear blisters of 28 x CHAMPIX 0.5 mg film-coated tablets in card packaging.
- A treatment initiation pack containing 2 blisters; 1 clear blister of 11 x CHAMPIX 0.5 mg film-coated tablets and 1 clear blister of 14 x CHAMPIX 1 mg film-coated tablets in a carton.
- A follow-on (maintenance) pack containing 2 clear blisters of 14 x CHAMPIX 1 mg film-coated tablets in a carton.
- A follow-on (maintenance) pack containing 4 clear blisters of 14 x CHAMPIX 1 mg film-coated tablets in a carton.
- A follow-on (maintenance) pack containing 8 clear blisters of 14 x CHAMPIX 1 mg film-coated tablets in a carton.
- A follow-on (maintenance) pack containing 10 clear blisters of 14 x CHAMPIX 1 mg film-coated tablets in a carton.
- A sealed white HDPE bottle pack, with a child resistant screw cap, in a carton, containing 56 x CHAMPIX 1 mg film-coated tablets.
- A sealed white HDPE bottle pack, with a child resistant screw cap, in a carton, containing 56 x CHAMPIX 0.5 mg film-coated tablets.

Not all pack sizes may be marketed.

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/