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 a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

0.5 mg film-coated tablets: 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

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.

CHAMPIX is for oral use. 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 start 1-2 weeks before this date.

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

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

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 (see section 5.1).

No data are available on the efficacy of an additional 12 weeks course of treatment for patients who do not succeed in stopping smoking during initial therapy or who relapse after treatment.

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).

Patients with renal insufficiency
No dosage adjustment is necessary for patients with mild (estimated creatinine clearance > 50 ml/min and ≤ 80 ml/min) to moderate (estimated creatinine clearance ≥ 30 ml/min and ≤ 50 ml/min) renal impairment.

For patients with moderate renal impairment who experience adverse events 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).

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

Dosing in elderly patients
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.

Paediatric patients
CHAMPIX is not recommended for use in children or adolescents below 18 years of age due to insufficient data on safety and efficacy (see section 5.2).

4.3 Contraindications

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

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.

Depression, suicidal ideation and behaviour and suicide attempts have been reported in patients attempting to quit smoking with Champix in the post-marketing experience. Not all patients had stopped smoking at the time of onset of symptoms and not all patients had known pre-existing psychiatric illnesss. Clinicians should be aware of the possible emergence of significant depressive symptomatology in patients undergoing a smoking cessation attempt, and should advise patients accordingly. Champix should be discontinued immediately if agitation, depressed mood or changes in behaviour that are of concern for the doctor, the patient, family or caregivers are observed, or if the patient develops suicidal ideation or suicidal behaviour.

Depressed mood, rarely including suicidal ideation and suicide attempt, may be a symptom of nicotine withdrawal. In addition, smoking cessation, with or without pharmacotherapy, has been associated with exacerbation of underlying psychiatric illness (e.g. depression).

The safety and efficacy of Champix in patients with serious psychiatric illness such as schizophrenia, bipolar disorder and major depressive disorder has not been established. Care should be taken with patients with a history of psychiatric illness and patients should be advised accordingly.

There is no clinical experience with CHAMPIX in patients with epilepsy.

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.

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 is limited clinical data on any potential interaction between alcohol and varenicline.

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 Pregnancy and lactation

There are no adequate data from the use of CHAMPIX in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. CHAMPIX should not be used during pregnancy.

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.

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

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 events associated with study drug treatment or those possibly associated with nicotine withdrawal.

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

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

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

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	
Uncommon	Bronchitis, nasopharyngitis, sinusitis, fungal infection, viral infection,.
Metabolism and nutrition disorders	
Common	Increased appetite
Uncommon	Anorexia, decreased appetite, polydipsia

System Organ Class	Adverse Drug Reactions
Psychiatric disorders	
Very common	Abnormal dreams, insomnia
Uncommon	Panic reaction, bradyphrenia, thinking abnormal, mood swings
Nervous system disorders	
Very common	Headache
Common	Somnolence, dizziness, dysgeusia
Uncommon	Tremor, coordination abnormal, dysarthria, hypertonia, restlessness, dysphoria, hypoaesthesia, hypogeusia, lethargy, libido increased, libido decreased
Cardiac disorders	
Uncommon	Atrial fibrillation, palpitations
Eye disorders	
Uncommon	Scotoma, scleral discolouration, eye pain, mydriasis, photophobia, myopia, lacrimation increased
Ear and labyrinth disorders	
Uncommon	Tinnitus
Respiratory, thoracic and mediastinal disorders	
Uncommon	Dyspnoea, cough, hoarseness, pharyngolaryngeal pain, throat irritation, respiratory tract congestion, sinus congestion, post nasal drip, rhinorrhoea, snoring
Gastrointestinal disorders	
Very common	Nausea
Common	Vomiting, constipation, diarrhoea, abdominal distension, stomach discomfort, dyspepsia, flatulence, dry mouth
Uncommon	Haematemesis, haematochezia, gastritis, gastrooesophageal reflux disease, abdominal pain, change of bowel habit, abnormal faeces, eructation, aphthous stomatitis, gingival pain, tongue coated
Skin and subcutaneous tissue disorders	
Uncommon	Rash generalised, erythema, pruritus, acne, hyperhidrosis, night sweats
Musculoskeletal and connective tissue disorders	
Uncommon	Joint stiffness, muscle spasms, chest wall pain, costochondritis
Renal and urinary disorders	
Uncommon	Glycosuria, nocturia, polyuria
Reproductive system and breast disorders	
Uncommon	Menorrhagia, vaginal discharge, sexual dysfunction
General disorders and administration site conditions	
Common	Fatigue
Uncommon	Chest discomfort, chest pain, pyrexia, feeling cold, asthenia, circadian rhythm sleep disorder, malaise, cyst
Investigations	
Uncommon	Blood pressure increased, electrocardiogram ST segment depression, electrocardiogram T wave amplitude decreased, heart rate increased, liver function test abnormal, platelet count decreased, weight increased, semen abnormal, C-reactive protein increased, blood calcium decreased

Post-marketing cases of myocardial infarction, depression and suicidal ideation have been reported in patients taking varenicline (see section 4.4). There have also been reports of hypersensitivity reactions, such as angioedema and facial swelling.

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: Active substances used in nicotine dependence, ATC code: N07BA03

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).

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

The efficacy of CHAMPIX in smoking cessation was demonstrated in 3 clinical trials involving chronic cigarette smokers (≥10 cigarettes per day). 2619 patients received CHAMPIX 1mg 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 randomized 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 randomized 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. The odds of maintaining abstinence at week 24, following an additional 12 weeks of treatment with CHAMPIX, were 2.47 times those for placebo (p<0.0001). Superiority to placebo for CA was maintained through week 52 (Odds Ratio=1.35, p=0.0126).

The key results are summarised in the following table:

	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)

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

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.

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 medications, as demonstrated in specific pharmacokinetic studies and in population pharmacokinetic analyses.

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

Renal Insufficiency: Varenicline pharmacokinetics were unchanged in subjects with mild renal impairment (estimated creatinine clearance > 50 ml/min and ≤ 80 ml/min). In patients with moderate renal impairment (estimated creatinine clearance ≥ 30 ml/min and ≤ 50 ml/min), varenicline exposure increased 1.5-fold compared with subjects with normal renal function (estimated creatinine clearance > 80 ml/min). In subjects with severe renal impairment (estimated creatinine clearance < 30 ml/min), varenicline exposure was increased 2.1-fold. In subjects with end-stage-renal disease (ESRD), varenicline was efficiently removed by 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.

Adolescents: When 22 adolescents aged 12 to 17 years (inclusive) received a single 0.5 mg and 1 mg dose of varenicline the pharmacokinetics of varenicline was approximately dose proportional between the 0.5 mg and 1 mg doses. Systemic exposure, as assessed by AUC (0-inf), and renal clearance of varenicline were comparable to adults. An increase of 30% in C_{max} and a shorter elimination half-life (10.9 hr) were observed in adolescents compared with adults (see section 4.2).

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.

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

Core Tablet

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

Film Coating

Hypromellose
Titanium Dioxide (E171)
Macrogols
Triacetin

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

Treatment initiation packs
Aclar / 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.

Aclar / 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.

Aclar / 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.

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

Aclar / 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) blue white tablet container 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 and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent
CT13 9NJ
UK

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/360/003
EU/1/06/360/008
EU/1/06/360/012
EU/1/06/360/006
EU/1/06/360/007
EU/1/06/360/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26/09/2006

10. DATE OF REVISION OF THE TEXT

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 a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

1 mg film-coated tablets: 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

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.

CHAMPIX is for oral use. The recommended dose is 1 mg varenicline twice daily following a 1-week titration as follows:

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

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

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

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

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 (see section 5.1).

No data are available on the efficacy of an additional 12 weeks course of treatment for patients who do not succeed in stopping smoking during initial therapy or who relapse after treatment.

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).

Patients with renal insufficiency
No dosage adjustment is necessary for patients with mild (estimated creatinine clearance > 50 ml/min and ≤ 80 ml/min) to moderate (estimated creatinine clearance ≥ 30 ml/min and ≤ 50 ml/min) renal impairment.

For patients with moderate renal impairment who experience adverse events 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).

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

Dosing in elderly patients
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.

Paediatric patients
CHAMPIX is not recommended for use in children or adolescents below 18 years of age due to insufficient data on safety and efficacy (see section 5.2).

4.3 Contraindications

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

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.

Depression, suicidal ideation and behaviour and suicide attempts have been reported in patients attempting to quit smoking with Champix in the post-marketing experience. Not all patients had stopped smoking at the time of onset of symptoms and not all patients had known pre-existing psychiatric illness. Clinicians should be aware of the possible emergence of significant depressive symptomatology in patients undergoing a smoking cessation attempt, and should advise patients accordingly. Champix should be discontinued immediately if agitation, depressed mood or changes in behaviour that are of concern for the doctor, the patient, family or caregivers are observed, or if the patient develops suicidal ideation or suicidal behaviour.

Depressed mood, rarely including suicidal ideation and suicide attempt, may be a symptom of nictotine withdrawal. In addition, smoking cessation, with or without pharmacotherapy, has been associated with the exacerbation of underlying psychiatric illness (e.g. depression).

The safety and efficacy of Champix in patients with serious psychiatric illness such as schizophrenia, bipolar disorder and major depressive disorder has not been established. Care should be taken with patients with a history of psychiatric illness and patients should be advised accordingly.

There is no clinical experience with CHAMPIX in patients with epilepsy.

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.

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 is limited clinical data on any potential interaction between alcohol and varenicline.

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 Pregnancy and lactation

There are no adequate data from the use of CHAMPIX in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. CHAMPIX should not be used during pregnancy.

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.

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

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 events associated with study drug treatment or those possibly associated with nicotine withdrawal.

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

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

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

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	
Uncommon	Bronchitis, nasopharyngitis, sinusitis, fungal infection, viral infection,.
Metabolism and nutrition disorders	
Common	Increased appetite
Uncommon	Anorexia, decreased appetite, polydipsia

System Organ Class	Adverse Drug Reactions
Psychiatric disorders	
Very common	Abnormal dreams, insomnia
Uncommon	Panic reaction, bradyphrenia, thinking abnormal, mood swings
Nervous system disorders	
Very common	Headache
Common	Somnolence, dizziness, dysgeusia
Uncommon	Tremor, coordination abnormal, dysarthria, hypertonia, restlessness, dysphoria, hypoaesthesia, hypogeusia, lethargy, libido increased, libido decreased
Cardiac disorders	
Uncommon	Atrial fibrillation, palpitations
Eye disorders	
Uncommon	Scotoma, scleral discolouration, eye pain, mydriasis, photophobia, myopia, lacrimation increased
Ear and labyrinth disorders	
Uncommon	Tinnitus
Respiratory, thoracic and mediastinal disorders	
Uncommon	Dyspnoea, cough, hoarseness, pharyngolaryngeal pain, throat irritation, respiratory tract congestion, sinus congestion, post nasal drip, rhinorrhoea, snoring
Gastrointestinal disorders	
Very common	Nausea
Common	Vomiting, constipation, diarrhoea, abdominal distension, stomach discomfort, dyspepsia, flatulence, dry mouth
Uncommon	Haematemesis, haematochezia, gastritis, gastrooesophageal reflux disease, abdominal pain, change of bowel habit, abnormal faeces, eructation, aphthous stomatitis, gingival pain, tongue coated
Skin and subcutaneous tissue disorders	
Uncommon	Rash generalised, erythema, pruritus, acne, hyperhidrosis, night sweats
Musculoskeletal and connective tissue disorders	
Uncommon	Joint stiffness, muscle spasms, chest wall pain, costochondritis
Renal and urinary disorders	
Uncommon	Glycosuria, nocturia, polyuria
Reproductive system and breast disorders	
Uncommon	Menorrhagia, vaginal discharge, sexual dysfunction
General disorders and administration site conditions	
Common	Fatigue
Uncommon	Chest discomfort, chest pain, pyrexia, feeling cold, asthenia, circadian rhythm sleep disorder, malaise, cyst
Investigations	
Uncommon	Blood pressure increased, electrocardiogram ST segment depression, electrocardiogram T wave amplitude decreased, heart rate increased, liver function test abnormal, platelet count decreased, weight increased, semen abnormal, C-reactive protein increased, blood calcium decreased

Post-marketing cases of myocardial infarction, depression and suicidal ideation have been reported in patients taking varenicline (see section 4.4). There have also been reports of hypersensitivity reactions, such as angioedema and facial swelling.

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: Active substances used in nicotine dependence, ATC code: N07BA03

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).

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

The efficacy of CHAMPIX in smoking cessation was demonstrated in 3 clinical trials involving chronic cigarette smokers (≥10 cigarettes per day). 2619 patients received CHAMPIX 1mg 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 randomized 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 randomized 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. The odds of maintaining abstinence at week 24, following an additional 12 weeks of treatment with CHAMPIX, were 2.47 times those for placebo (p<0.0001). Superiority to placebo for CA was maintained through week 52 (Odds Ratio=1.35, p=0.0126).

The key results are summarised in the following table:

	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)

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

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.

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 medications, as demonstrated in specific pharmacokinetic studies and in population pharmacokinetic analyses.

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

Renal Insufficiency: Varenicline pharmacokinetics were unchanged in subjects with mild renal impairment (estimated creatinine clearance > 50 ml/min and ≤ 80 ml/min). In patients with moderate renal impairment (estimated creatinine clearance ≥ 30 ml/min and ≤ 50 ml/min), varenicline exposure increased 1.5-fold compared with subjects with normal renal function (estimated creatinine clearance > 80 ml/min). In subjects with severe renal impairment (estimated creatinine clearance < 30 ml/min), varenicline exposure was increased 2.1-fold. In subjects with end-stage-renal disease (ESRD), varenicline was efficiently removed by 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.

Adolescents: When 22 adolescents aged 12 to 17 years (inclusive) received a single 0.5 mg and 1 mg dose of varenicline the pharmacokinetics of varenicline was approximately dose proportional between the 0.5 mg and 1 mg doses. Systemic exposure, as assessed by AUC (0-inf), and renal clearance of varenicline were comparable to adults. An increase of 30% in C_{max} and a shorter elimination half-life (10.9 hr) were observed in adolescents compared with adults (see section 4.2).

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.

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

Core Tablet

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

Film Coating

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

Treatment initiation packs
Aclar / 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.

Aclar / 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.

Aclar / 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.

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

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

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

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

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

High-density polyethylene (HDPE) blue white tablet container 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 and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent
CT13 9NJ
UK

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/360/003
EU/1/06/360/008
EU/1/06/360/012
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/1/06/360/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26/09/2006

10. DATE OF REVISION OF THE TEXT

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

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

Pfizer Manufacturing Deutschland GmbH
Heinrich-Mack-Strasse 35
D-89257 Illertissen
Germany

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to medical prescription.

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

- **OTHER CONDITIONS**

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance, as described in Version 1.1 presented in Module 1.8.1. of the Marketing Authorisation, is in place and functioning before and whilst the product is on the market.

Risk Management Plan

The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 3.0 (25 June 2008) of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, any updated RMP should be submitted at the same time as the following Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the EMEA

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

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 and 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.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not use if box has been opened

KEEP THE PACKAGE INTACT

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
Sandwich
Kent
CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/360/003

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

START AT DAY 1
The day I stop smoking should be between day 8 and day 14.
The day I stop smoking will be _____.

Week 1
Week 2

Numbers 1 to 14
sun as symbol
moon as symbol

16. INFORMATION IN BRAILLE

CHAMPIX
0.5 mg
1 mg

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: MM/YYYY

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: MM/YYYY

4. BATCH NUMBER

Lot:

5. OTHER

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.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not use if box has been opened

KEEP THE PACKAGE INTACT

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
Sandwich
Kent
CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/360/012

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

START AT DAY 1
The day I stop smoking should be between day 8 and day 14.
The day I stop smoking will be _____.

Week 1
Week 2
Week 3
Week 4

Numbers 1 to 28
sun as symbol
moon as symbol

16. INFORMATION IN BRAILLE

CHAMPIX
0.5 mg
1 mg

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

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

28 film-coated tablets
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 REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not use if box has been opened

KEEP THE PACKAGE INTACT

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
Sandwich
Kent
CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/360/004
EU/1/06/360/005

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

numbers 1 to 14
numbers 1 to 28
sun as symbol
moon as symbol

16. INFORMATION IN BRAILLE

CHAMPIX 1 mg

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
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

28 film-coated tablets
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 REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not use if box has been opened

KEEP THE PACKAGE INTACT

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
Sandwich
Kent
CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/360/006
EU/1/06/360/007

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

numbers 1 to 14
numbers 1 to 28
sun as symbol
moon as symbol

16. INFORMATION IN BRAILLE

CHAMPIX 0.5 mg

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

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 and 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.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not use if box has been opened

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
Sandwich
Kent
CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/360/008

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

CHAMPIX
0.5 mg
1 mg

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

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*

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

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 REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not use if box has been opened

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
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

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

CHAMPIX 1 mg

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

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 REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not use if box has been opened

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
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

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

CHAMPIX 1 mg

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 REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not use if box has been opened

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
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

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

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 REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not use if box has been opened

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
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

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

CHAMPIX 0.5 mg

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 REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not use if box has been opened

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
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

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

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.

- 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. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT CHAMPIX IS AND WHAT IT IS USED FOR

CHAMPIX is a a non-nicotine medicine which is used to help you stop smoking.

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

Although you are not recommended to smoke after your quit date, CHAMPIX can also reduce the enjoyment of cigarettes if you do smoke when on treatment. (The quit date is the day in the second week of treatment when you will stop smoking, see Section 3.)

2. BEFORE YOU TAKE CHAMPIX

Do not take CHAMPIX

- If you are allergic (hypersensitive) to varenicline tartrate or any of the other ingredients of CHAMPIX

Take special care with CHAMPIX

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

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 drugs work. Therefore, in some cases an adjustment of the dose

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.

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

Depressed mood may appear during smoking cessation with or without treatment. Depression, rarely including suicidal thoughts and suicide attempt, has been reported in patients undergoing a smoking cessation attempt. These feelings have also been reported while attempting to quit smoking with Champix.
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.

Effect of CHAMPIX on other drugs
CHAMPIX is not expected to affect the way other drugs work.

Effect of other drugs on CHAMPIX
Due to the way in which varenicline tartrate is removed from the body, it is not expected that other drugs will affect the way in which CHAMPIX works.

Use of CHAMPIX with other therapies for smoking cessation
The safety and benefits of taking CHAMPIX in combination with other medicines for stopping smoking have not been studied. CHAMPIX in combination with other smoking cessation therapies is therefore not recommended.

CHAMPIX is not recommended for use in children or adolescents below 18 years.

Taking CHAMPIX with food and drink

CHAMPIX can be taken with or without food.

Pregnancy

You should not take CHAMPIX while you are pregnant.

Talk to your doctor if you are intending to become pregnant. If you want to start treatment with CHAMPIX, your treatment should be timed so that you have completed the course before becoming pregnant.

Breast-feeding

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 medication affects your ability to perform these activities.

3. HOW TO TAKE CHAMPIX

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.

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

Before starting your course of CHAMPIX you should decide on a date in the second week of treatment (between day 8 and day 14) when you will stop smoking. You should write this date on the pack as a reminder.

CHAMPIX tablets should be swallowed whole with water.

The usual dose for adults which you should follow from Day 1 is described in the following table:

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.

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.

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.

In smoking cessation therapy, risk of returning to smoking may be elevated in the period immediately following the end of treatment. Your doctor may decide to gradually lower your dose of CHAMPIX at the end of treatment.

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

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 almost time for 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.

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

4. POSSIBLE SIDE EFFECTS

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.

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

- Very common side effects which may affect more than 1 person in 10 are listed below:
    - Headache, difficulty sleeping, abnormal dreams
    - Nausea
- Common side effects which may affect more than 1 person in 100 are listed below:
    - Increased appetite, changes in the way things taste, dry mouth
    - Sleepiness, tiredness, dizziness
    - Vomiting, constipation, diarrhoea, feeling bloated, stomach discomfort, indigestion, flatulence
- Uncommon side effects which may affect more than 1 person in 1, 000 are listed below:
    - Chest infection, discomfort or pain, inflammation of the sinuses,
    - Fever, feeling cold, feeling weak or unwell, viral infection, shortness of breath, cough, hoarseness, throat pain and irritation, congested sinuses, runny nose, snoring
    - Loss of appetite, feeling thirsty, increased weight
    - Feeling of panic, difficulty thinking, mood swings
    - Tremor, difficulty with coordination, difficulty with speech, less sensitive to touch, increased muscle tension, restlessness,
    - Heart rhythm disturbances, increased blood pressure, increased heart rate
    - Disturbed vision, eyeball discolouration, eye pain, dilated pupils, shortsightedness, sensitivity to light, watery eyes
    - Ringing in the ears
    - Blood in vomit, irritated stomach and heartburn, abdominal pain, abnormal stools, red blood in stools, belching, mouth ulcers, pain in the gums, coated tongue
    - Skin rash, cyst, fungal infection, reddening of the skin, itching, acne, increased sweating
    - Chest wall and rib pain, stiff joints, muscle spasms
    - Glucose in urine, increased urine volume and frequency
    - Increased menstrual flow, vaginal discharge, changes in sex drive or ability

- There have been reports of heart attack, depression, suicidal thoughts and hypersensitivity reactions (such as swollen face or tongue) in patients attempting to quit smoking with CHAMPIX.

If you are taking Champix and develop agitation, depressed mood, changes in behaviour or suicidal thoughts you should stop your treatment and contact your doctor immediately.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE CHAMPIX

Keep out of the reach and sight of children.

Do not use CHAMPIX after the expiry date which is stated on the card packaging or carton. The expiry date refers to the last day of that month.
This medicine does not require any special storage conditions.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What CHAMPIX contains

- The active substance is 0.5 mg varenicline and 1 mg varenicline respectively
- 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) Macrogols Triacetin

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

What CHAMPIX 0.5 mg and 1 mg film-coated tablets look 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:

Not all pack sizes may be marketed.

- 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 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 sealed blue white HDPE bottle pack, with a child resistant screw cap, in a carton, containing 56 x CHAMPIX 1 mg film-coated tablets.
- A sealed blue white HDPE bottle pack, with a child resistant screw cap, in a carton, containing 56 x CHAMPIX 0.5 mg film-coated tablets.

Marketing Authorisation Holder

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CT13 9NJ
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This leaflet was last approved in.

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