PRODUCT INFORMATION

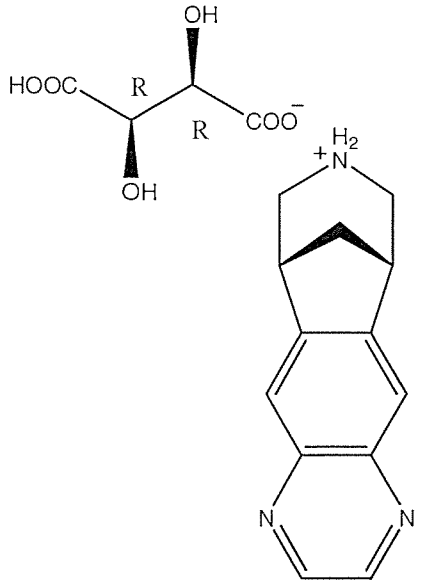
CHAMPIX® (varenicline as tartrate)

NAME OF THE MEDICINE

CHAMPIX® 0.5 mg and 1 mg film-coated tablets

DESCRIPTION

Varenicline tartrate powder is a white to off-white to slightly yellow solid with the following chemical name: 7,8,9,10-tetrahydro-6,10-methano-6*H*-pyrazino[2,3-h][3]benzazepine, (2*R*,3*R*)-2,3-dihydroxybutanedioate (1:1). It is highly soluble in water. The pKa (ionisation constant) for varenicline is 9.2. The octanol-water partition coefficient (Log D) of varenicline tartrate is -1.23 at pH 5, -0.817 at pH 7 and 0.758 at pH 9. Varenicline tartrate has a molecular weight of 361.35 Daltons, and a molecular formula of $C_{13}H_{13}N_3 \bullet C_4H_6O_6$. The chemical structure is:



CAS No: 375815-87-5

CHAMPIX is supplied for oral administration in two strengths: a 0.5 mg capsular biconvex, white to off-white, film-coated tablet debossed with "*Pfizer*" on one side and "CHX 0.5" on the other side and a 1 mg capsular biconvex, light blue film-coated tablet debossed with "*Pfizer*" on one side and "CHX 1.0" on the other side. Each film-coated tablet of varenicline contains the appropriate amount of varenicline as the tartrate salt and the following inactive ingredients: microcrystalline cellulose, calcium hydrogen phosphate anhydrous, croscarmellose sodium, silica – colloidal anhydrous, magnesium stearate, Opadry® White (for 0.5 mg), Opadry® Blue (for 1 mg), and Opadry® Clear.

PHARMACOLOGY

Pharmacological actions

Pharmacotherapeutic group: Drugs used in nicotine dependence, ATC code: *N07BA*

Varenicline is a partial agonist at α4β2 neuronal nicotinic acetylcholine receptors where it binds with high affinity and selectivity to produce an effect sufficient to alleviate symptoms of craving and withdrawal (agonist activity), while simultaneously resulting in blockade of the rewarding and reinforcing effects of smoking by preventing nicotine binding to α4β2 receptors (antagonist activity).

Electrophysiology studies *in vitro* and neurochemical studies *in vivo* have shown that varenicline binds to α4β2 neuronal nicotinic acetylcholine receptors and stimulates receptor-mediated activity. The maximal activity of varenicline was approximately 30-50% that of nicotine in vitro and ranged from 30-60% that of nicotine in vivo. Varenicline blocks the ability of nicotine to activate the α4β2 receptor and thus to stimulate the central nervous mesolimbic dopamine system, the neuronal mechanism underlying reinforcement and reward experienced upon smoking. Varenicline is highly selective and binds with higher affinity to the α4β2 receptor subtype than to other common nicotinic receptors (>500-fold α3β4, >3,500-fold α7, >20,000-fold α1βγδ), or to non-nicotinic receptors and transporters (>2,000-fold).

PHARMACOKINETICS

Absorption

Maximum plasma concentrations of varenicline tartrate occur typically within 3-4 hours after oral administration. Mean (SD) C_{max} was 9.22 (2.05) ng/mL at the recommended dose of 1 mg BID. Following administration of multiple oral doses to healthy volunteers, steady-state conditions were reached within 4 days. Varenicline tartrate exhibits linear kinetics when given as single or repeated doses. Absorption is virtually complete after oral administration and systemic availability is high. Oral bioavailability of varenicline tartrate is unaffected by food or time-of-day dosing.

Distribution

Plasma protein binding of varenicline tartrate is low (<20%) and independent of both age and renal function. Apparent volume of distribution averaged 415 litres (%CV= 50) at steady-state.

Metabolism

Varenicline tartrate undergoes minimal metabolism with 92% eliminated unchanged in the urine.

Elimination

The elimination half-life of varenicline tartrate is approximately 24 hours (individual range 10-58 hr). Renal elimination of varenicline tartrate is primarily through glomerular filtration along with active tubular secretion via the organic cationic transporter, OCT2.

Pharmacokinetics in special patient populations

There are no clinically meaningful differences in varenicline tartrate 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 insufficiency and the potential for clinically meaningful drug interactions between varenicline and metabolic inhibitors/inducers is low.

Renal Impairment

Varenicline tartrate pharmacokinetics were unchanged in subjects with mild renal impairment (estimated creatinine clearance >50ml/min and ≤80ml/min); in patients with moderate renal impairment (estimated creatinine clearance ≥30ml/min and ≤50ml/min), varenicline tartrate exposure increased 1.5-fold compared with subjects with normal renal function (estimated creatinine clearance >80ml/min). In subjects with severe renal impairment (estimated creatinine clearance <30ml/min), varenicline tartrate exposure increased 2.1-fold. In subjects with end-stage-renal disease (ESRD), varenicline tartrate was efficiently removed by haemodialysis. While no dosing adjustment is necessary for patients with mild to moderate renal impairment, a reduced dosing frequency of 1 mg once daily is recommended for patients with severe renal impairment (see **DOSAGE AND ADMINISTRATION**). Dosing should begin at 0.5 mg once daily for the first 3 days, and then increased to 1 mg once daily.

Elderly

No dosage adjustment is necessary for elderly patients (see **DOSAGE AND ADMINISTRATION**).

A combined single and multiple-dose pharmacokinetic study demonstrated that the pharmacokinetics of 1 mg varenicline tartrate given once or twice daily to 16 healthy elderly male and female smokers (aged 65-75 yrs) for 7 consecutive days was similar to that of younger subjects.

Paediatric

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

When 22 paediatric patients aged 12 to 17 years (inclusive) received a single 0.5 mg and 1 mg dose of varenicline tartrate the pharmacokinetics of varenicline tartrate 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 tartrate were comparable to those of an adult population.

CLINICAL TRIALS

The efficacy of CHAMPIX in smoking cessation was demonstrated in three clinical trials in which a total of 2619 chronic cigarette smokers (≥10 cigarettes per day) received varenicline.

Two of these studies were double-blind comparisons between varenicline, bupropion and placebo, assessing critical aspects of smoking cessation, including end-of-treatment and long-term abstinence rates after 12 weeks of treatment. In addition, the effects on reducing craving and withdrawal that can occur during smoking cessation and the reinforcing effects that can perpetuate smoking behaviour were studied. The third study assessed the effect of an additional 12 weeks of treatment on maintaining long-term abstinence.

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. Patients were treated for 12 weeks and then were followed up for a total study duration of 52 weeks. The CHAMPIX dosage of 1 mg twice daily was achieved using a titration of 0.5 mg once daily for the initial 3 days followed by 0.5 mg twice daily for the next 4 days. The bupropion dosage of 150 mg twice daily was achieved using a 3-day titration of 150 mg once daily. Patients set a date to stop smoking (target quit date, TQD) with dosing starting 1-2 weeks before this date.

The primary endpoint of the two studies was the carbon monoxide (CO) confirmed, 4-week continuous quit rate (4W-CQR) from week 9 through week 12. The quit rates are the proportions of all patients treated (i.e., intent-to-treat analysis) who abstained from smoking. The primary endpoint for CHAMPIX demonstrated statistical superiority to bupropion and placebo. Key secondary endpoints for both studies were Continuous Abstinence (CA) from weeks 9-52 and the Long Term Quit Rate (LTQR) at week 52. CA was defined as the proportion of all subjects who did not smoke (not even a puff of a cigarette) from Week 9 through Week 52 and had an exhaled CO measurement of ≤10ppm. LTQR was defined as the proportion of all subjects treated who were responders for the primary endpoint in the treatment phase and had no more than 6 days of cigarette smoking during the non-treatment phase.

In both studies the CO-confirmed 4-week CQR for week 9 through week 12 was superior ($p<0.0001$) for patients given CHAMPIX compared with the placebo and bupropion groups. Based on this endpoint, the odds of stopping on CHAMPIX were 3.91 (95% CI: 2.74, 5.59) and 3.85 (2.69, 5.50) times those of stopping on placebo in Studies 1 and 2 respectively; the odds of stopping on CHAMPIX were 1.96 (1.42, 2.72) to 1.89 (1.37, 2.61) times those of stopping on bupropion.

The 4W-CQR (weeks 9-12), and CA (weeks 9-52) and LTQR (week 52) from studies 1 and 2 are included in the following table:

Table 1 Continuous Quit Rates, Continuous Abstinence and Long Term Quit Rates for Studies 1 and 2						
	Study 1 n=1022			Study 2 n=1023		
	4W CQR	CA wk 9-52	LTQR wk 52	4W CQR	CA wk 9-52	LTQR wk 52
Champix	44.4%[a]	22.1%[b]	25.5%[c]	44.0%[a]	23.0%[d]	25.4%[e]
Bupropion	29.5%	16.4%	17.9%	30.0%	15.0%	18.2%
Placebo	17.7%	8.4%	9.6%	17.7%	10.3%	12.6%

[a] p <0.0001 vs. placebo and bupropion
[b] p <0.0001 vs. placebo, p=0.0640 vs. bupropion
[c] p <0.0001 vs. placebo, p=0.0161 vs. bupropion
[d] p <0.0001 vs. placebo, p=0.0062 vs. bupropion
[e] p <0.0001 vs. placebo, p=0.0205 vs. bupropion

Based on the key secondary endpoint of carbon monoxide confirmed (not even a puff of a cigarette) Continuous Abstinence from week 9 through week 52 (CA weeks 9-52), the odds of stopping on CHAMPIX were 2.66 (95% CI: 1.72, 4.11) and 3.13 (1.97, 4.97) times those of stopping on placebo in Studies 1 and 2 respectively.

For the LTQR at 52 weeks the odds of stopping smoking on CHAMPIX were 3.30 (2.13, 5.11) and 2.40 (1.60, 3.60) times those of stopping on placebo in Studies 1 and 2, respectively.

In Studies 1 and 2, three aspects of smoking cessation were investigated using validated Patient Reported Outcomes questionnaires: Craving, measured by Brief Questionnaire of Smoking Urges (QSU-Brief) and Minnesota Nicotine Withdrawal Scale (MNWS) Urge to Smoke item; Withdrawal, measured by 4 MNWS subscales; and Reinforcing Effects of Smoking, measured by five Modified Cigarette Evaluation Questionnaire (mCEQ) subscales.

Patient reported craving, withdrawal and reinforcing effects of smoking

Across both Studies 1 and 2, 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.

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. The two key secondary endpoints were the continuous abstinence (CA) rate for week 13 through week 52 and the long-term quit rate (LTQR) at week 52. The key results are summarised in the following table:

Table 2. Continuous Abstinence and Long term Quite Rates for Maintenance of Abstinence Study		
	CHAMPIX n=602	Placebo n=604
CA wk 13-24	70.6%*	49.8%
CA wk 13-52	44.0%**	37.1%
LTQR at week 52	47.8%***	40.7%
*p<0.0001 vs placebo, **p=0.0126 vs placebo, ***p=0.0119 vs placebo		

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 maintained abstinence at week 24, following an additional 12 weeks of treatment with CHAMPIX, were 2.47 times those for placebo (95% CI: 1.95, 3.15). Superiority to placebo for continuous abstinence was maintained through week 52 (Odds Ratio = 1.35, 95% CI: 1.07, 1.70).

INDICATIONS

CHAMPIX is indicated as an aid to smoking cessation in adults over the age of 18 years.

CONTRAINDICATIONS

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

PRECAUTIONS

Effects of Smoking Cessation:

Physiological changes resulting from smoking cessation, with or without treatment with CHAMPIX, may alter pharmacokinetics or pharmacodynamics of some drugs, 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.

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

Effects on ability to drive and use machines

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

Effects on Fertility

It is not expected that varenicline tartrate would impair fertility. Varenicline did not impair fertility in rats at oral doses producing plasma concentrations up to 40 times the human plasma C_{max} at the maximal recommended dose of 1 mg twice daily. Offspring of treated rats have shown decreased fertility (see **Use in Pregnancy**).

Use in Pregnancy

Pregnancy Category: B3

The safety of varenicline tartrate in human pregnancy has not been established. The use of CHAMPIX in pregnant women is not recommended.

There was no evidence of teratogenicity following oral administration of varenicline to rats and rabbits during organogenesis with systemic exposure (plasma AUC) up to 36 times the human plasma AUC at the maximal recommended dose of 1 mg twice daily.

In animal reproduction studies, varenicline has been shown to have adverse effects on the foetus and offspring. Oral administration of varenicline to pregnant rabbits during organogenesis resulted in reduced foetal weights at systemic exposure (plasma AUC) 50 times the human plasma AUC at the maximal recommended dose; the no-effect exposure was 23 times the clinical exposure. Oral administration of varenicline to pregnant rats from early gestation until weaning resulted in reduced fertility, increased auditory startle response and decreased rearing in offspring at maternal plasma concentrations 40 times the human plasma C_{max} at the maximal recommended dose; the no-effect exposure was 17 times clinical exposure.

Women of child bearing potential: Where drug therapy is initiated, treatment should be timed such that the course is completed before conception.

Use in Lactation

It is not known whether varenicline is excreted in human milk. Because many drugs are excreted in human milk and because the potential for adverse reactions in nursing infants from CHAMPIX is unknown, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Varenicline is excreted in the milk of lactating rats. Oral administration of varenicline to pregnant rats from early gestation until weaning was associated with adverse effects in offspring (see **Use in Pregnancy**). The clinical significance of this finding is unknown.

Carcinogenicity

Carcinogenicity studies were performed in mice and rats at respective oral doses of varenicline up to 20 mg/kg/day and 15 mg/kg/day for 2 years, with respective systemic drug exposure (C_{max}) up to 130 and 50 times the human plasma C_{max} at the maximal recommended dose of

1 mg twice daily. There was no evidence of a carcinogenicity in mice or female rats. Male rats showed increased incidences of hibernoma (a rare tumour of brown fat) at systemic exposures of 25 times the human C_{max} (incidence 1/65 rats) and 50 times the human C_{max} (incidence 2/65 rats); the no-effect exposure was 10 times the human C_{max}. The clinical relevance of this finding has not been established.

Genotoxicity

Varenicline had no genotoxic effects, with or without metabolic activation, based on the following assays: Ames bacterial mutation assay; mammalian CHO/HGPRT assay; and tests for cytogenic aberrations *in vivo* in rat bone marrow and *in vitro* in human lymphocytes.

INTERACTIONS WITH OTHER MEDICINES

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

In vitro studies demonstrate that varenicline tartrate does not inhibit cytochrome P450 enzymes (IC_{50}> 6,400 ng/ml). The P450 enzymes tested for inhibition were: 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4/5. Also, in human hepatocytes *in vitro*, varenicline was shown not to induce the activity of cytochrome P450 enzymes 1A2 and 3A4. Therefore, varenicline tartrate is unlikely to alter the pharmacokinetics of compounds that are primarily metabolised by cytochrome P450 enzymes.

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

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

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

Cimetidine: Co-administration of an OCT2 inhibitor, cimetidine (300 mg four times daily), with varenicline (2 mg single dose) increased the systemic exposure of varenicline by 29% due to a reduction in varenicline renal clearance. 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 tartrate (1 mg twice daily) did not alter the steady-state pharmacokinetics of digoxin administered as a 0.25 mg daily dose.

Warfarin: Varenicline tartrate (1 mg twice daily) did not alter the pharmacokinetics of a single 25 mg dose of (R,S)-warfarin. Prothrombin time (INR) was not affected by varenicline tartrate. Smoking cessation itself may result in changes to warfarin pharmacokinetics (see **PRECAUTIONS**).

Use with other therapies for smoking cessation:

Bupropion: Varenicline tartrate (1 mg twice daily) did not alter the steady-state pharmacokinetics of bupropion (150 mg twice daily).

Nicotine replacement therapy (NRT): When varenicline (1 mg twice daily) and nicotine replacement therapy (transdermal 21 mg/day) were co-administered to smokers (N=24) for 12 days, there was a statistically significant decrease in average systolic blood pressure (mean 2.6 mmHg) measured on the final day of the study. In this study, the incidence of nausea, headache, vomiting, dyspepsia, fatigue and dizziness 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.

ADVERSE REACTIONS

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

The treatment discontinuation rate 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% 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)

Table 3 includes the most frequently occurring events (at a rate of ≥1% and an incidence higher than that for placebo). These data are derived from a pooled database of studies in which patients were randomised to receive 12 weeks of treatment using the recommended dosage regimen.

Table 3. Adverse Events considered treatment-related and reported in studies at a rate ≥1% and at an incidence higher than placebo, conducted using the recommended dosage regimen		
	Percentage of patients reporting event	
	CHAMPIX N=821	Placebo N=805
Gastrointestinal Disorders		
Nausea	28.6	8.8
Constipation	5.8	2.2
Flatulence	5.1	2.5
Dry mouth	5.6	4.1
Dyspepsia	3.8	1.5
Vomiting	4.1	0.7
Abdominal distension	1.3	0.4
Stomach discomfort	1.1	0.5
General Disorders and Administration Site Conditions		
Fatigue	4.6	3.9
Metabolism and nutrition disorders		
Increased appetite	1.7	1.2
Nervous System Disorders		
Headache	10.1	8.4
Dizziness	5.2	4.6
Dysgeusia	5.0	3.6
Somnolence	3.0	2.1
Psychiatric Disorders		
Insomnia	13.8	10.6
Abnormal dreams	12.4	4.5
Sleep disorder	4.8	2.9

In the table below all adverse reactions, which occurred at a rate lower than 1% and greater than placebo are listed by system organ class and frequency (uncommon (>1/1,000, <1/100)).

System Organ Class	Adverse Drug Reactions
Infections and Infestations	
Uncommon	Bronchitis, nasopharyngitis, sinusitis, fungal infection, viral infection
Metabolism and nutrition disorders	
Uncommon	Anorexia, decreased appetite, polydipsia
Psychiatric disorders	
Uncommon	Panic reaction, bradyphrenia, thinking abnormal, mood swings
Nervous system disorders	
Uncommon	Tremor, coordination abnormal, dysarthria, hypertonia, restlessness,

System Organ Class	Adverse Drug Reactions
	dysphoria, hypoaesthesia, hypogeusia, lethargy, libido increased, libido decreased
Cardiac disorders	
Uncommon	Atrial fibrillation, palpitations
Vascular Disorders	
Uncommon	Hot flush, varicose vein
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	
Uncommon	Haematemesis, haematochezia, gastritis, gastrooesophageal reflux disease, abdominal pain, change of bowel habit, salivary hypersecretion, 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	
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

DOSAGE AND ADMINISTRATION

Use in Adults

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

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

Days 1 – 3:	0.5 mg one 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.

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 is recommended to further increase the likelihood of long-term abstinence.

Patients who do not succeed in stopping smoking during 12 weeks of initial therapy, or who relapse after treatment, should be encouraged to make another attempt once factors contributing to the failed attempt have been identified and addressed.

Dose tapering of CHAMPIX is not required at the end of treatment.

Use in patients with renal impairment

No dosage adjustment is necessary for patients with mild to moderate renal impairment.

For patients with severe renal impairment, 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 (see **PHARMACOKINETICS**)

Based on insufficient clinical experience with Champix in patients with end stage renal disease, treatment is not recommended in this patient population (see "**Pharmacokinetics in special patient populations**").

Use in patients with hepatic impairment

No dosage adjustment is necessary for patients with hepatic impairment (see **PHARMACOKINETICS**)

Use in the elderly

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

Use in children

Safety and effectiveness of CHAMPIX in paediatric patients have not been established; therefore, CHAMPIX is not recommended for use in patients under 18 years of age (see **PHARMACOKINETICS**).

OVERDOSAGE

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 dialysed in patients with end stage renal disease (see **PHARMACOKINETICS**), however, there is no experience in dialysis following overdose.

Contact the Poisons Information Centre for advice on the management of an overdose.

PRESENTATION AND STORAGE CONDITIONS

Shelf Life: 2 years

Carton containing 11 x 0.5 mg film-coated tablets and 42 x 1 mg film-coated tablets in Aclar / PVC / blisters with aluminium foil backing packaging. This carton contains two heat sealed cards. The first heat sealed card consists of an initial dosing pack containing one blister of 11 x 0.5 mg tablets and a second blister of 14 x 1 mg tablets. The second heat sealed card consists of 28 x 1 mg tablets.

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

Aclar / PVC / blisters with aluminium foil backing in an initial dosing pack containing one blister of 11 x 0.5 mg film-coated tablets and a second blister of 14 x 1 mg film-coated tablets in a carton or a heat sealed card packaging. (Not currently marketed in Australia).

Aclar / PVC blisters with aluminium foil backing in a pack containing 28 or 140 x 1 mg film-coated tablets in a carton or secondary heat sealed card packaging. (Not currently marketed in Australia).

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 currently marketed in Australia).

NAME AND ADDRESS OF THE SPONSOR

Pfizer Australia Pty Ltd

ABN 50 008 422 348

38 – 42 Wharf Road

West Ryde NSW 2114

POISON SCHEDULE

S4-PRESCRIPTION ONLY MEDICINE

DATE OF APPROVAL

Approved by the Therapeutic Goods Administration on 15 February 2007.

Date of most recent amendment: 05 September 2007.