

# DATA SHEET

## CHAMPIX<sup>®</sup>

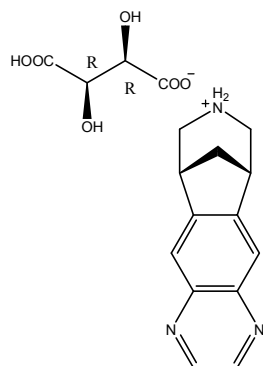
(varenicline as tartrate)

### PRODUCT NAME

CHAMPIX<sup>®</sup> 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<sub>13</sub>H<sub>13</sub>N<sub>3</sub> • C<sub>4</sub>H<sub>6</sub>O<sub>6</sub>. 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<sup>®</sup> White (for 0.5 mg), Opadry<sup>®</sup> Blue (for 1 mg), and Opadry<sup>®</sup> Clear.

# PHARMACOLOGY

## Pharmacodynamics

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

Varenicline is a partial agonist activity at  $\alpha 4\beta 2$  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  $\alpha 4\beta 2$  receptors (antagonist activity).

Electrophysiology studies *in vitro* and neurochemical studies *in vivo* have shown that varenicline binds to the  $\alpha 4\beta 2$  neuronal nicotinic acetylcholine receptors and stimulates receptor-mediated activity. The maximal activity of varenicline was approximately 30-50% that of nicotine *in vitro* and approximately 30% that of nicotine *in vivo*. Varenicline blocks the ability of nicotine to activate the  $\alpha 4\beta 2$  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  $\alpha 4\beta 2$  receptor subtype than to other common nicotinic receptors (>500-fold  $\alpha 3\beta 4$ , >3,500-fold  $\alpha 7$ , >20,000-fold  $\alpha 1\beta\gamma\delta$ ), 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  $>50\text{ml/min}$  and  $\leq 80\text{ml/min}$ ); in patients with moderate renal impairment (estimated creatinine clearance  $\geq 30\text{ml/min}$  and  $\leq 50\text{ml/min}$ ), varenicline tartrate exposure increased 1.5-fold compared with subjects with normal renal function (estimated creatinine clearance  $>80\text{ml/min}$ ). In subjects with severe renal impairment (estimated creatinine clearance  $<30\text{ml/min}$ ), 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 (> 65 years)***

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 1mg 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.

#### ***Children and Adolescents***

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 ( $\geq 10$  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  $>10$ ppm. 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% <sup>a</sup>	22.1% <sup>b</sup>	25.5% <sup>c</sup>	44.0% <sup>a</sup>	23.0% <sup>d</sup>	25.4% <sup>e</sup>
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%

<sup>a</sup> p <0.0001 vs. placebo and bupropion

<sup>b</sup> p <0.0001 vs. placebo, p=0.0640 vs. bupropion

<sup>c</sup> p <0.0001 vs. placebo, p=0.0161 vs. bupropion

<sup>d</sup> p <0.0001 vs. placebo, p=0.0062 vs. bupropion

<sup>e</sup> 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 Quit 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.

## 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.

### **Psychiatric Symptoms**

Serious neuropsychiatric symptoms have occurred in patients being treated with CHAMPIX. Some cases may have been complicated by the symptoms of nicotine withdrawal in patients who stopped smoking; however, some of these symptoms have occurred in patients who continued to smoke. Although a causal association between CHAMPIX and these symptoms has not been established, in some reports the association cannot be excluded. Patients being treated with CHAMPIX and their families, should be alerted to the need to monitor for neuropsychiatric symptoms including changes in behaviour or thinking, anxiety, psychosis, mood swings, agitation, aggression, depressed mood, suicidal ideation and suicidal behaviour. Doctors should discuss the efficacy and safety profile of CHAMPIX with patients attempting to quit smoking with CHAMPIX and advise them of the possible emergence of neuropsychiatric symptoms. These symptoms, as well as worsening of pre-existing psychiatric illness, have been reported in patients attempting to quit smoking while taking CHAMPIX in the post-marketing experience. Patients and their families, should be advised that the patient should stop taking CHAMPIX and contact a health care professional immediately if changes in behaviour or thinking, agitation or depressed mood, that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behaviour. In many post-marketing cases, resolution of symptoms after discontinuation of CHAMPIX was reported, although in some cases the symptoms persisted; therefore, ongoing follow up should be provided until symptoms resolve. Patients and their families should be encouraged to report any history of psychiatric illness prior to initiating treatment. Patients with serious psychiatric illness such as schizophrenia, bipolar disorder, and major depressive disorder did not participate in the pre-marketing studies of CHAMPIX and the safety and efficacy of CHAMPIX in such patients has not been established.

There have been post-marketing reports of hypersensitivity reactions including angioedema in patients treated with CHAMPIX. Clinical signs included swelling of the face, mouth (tongue, lips and gums), neck (throat and larynx) and extremities. There were rare reports of life-threatening angioedema requiring urgent medical attention due to respiratory compromise. Patients experiencing these symptoms should discontinue treatment with CHAMPIX and contact a health care provider immediately (see **ADVERSE EFFECTS, Post-Marketing Experience**).

There have also been post-marketing reports of rare but severe cutaneous reactions, including Stevens-Johnson Syndrome and Erythema Multiforme in patients using CHAMPIX. As these skin reactions can be life-threatening, patients should discontinue treatment at the first sign of rash or skin reaction and contact a healthcare provider immediately (see **ADVERSE EFFECTS, Post-Marketing Experience**).

### **Effects on Ability to Drive and Use Machines**

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

## 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 (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 effects 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.

## 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 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 varenicline as the increase in systemic exposure to varenicline tartrate is not expected to be clinically meaningful (see cimetidine interaction below). Furthermore since metabolism of varenicline 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 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 effects 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 effects.

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  $\geq 1\%$  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  $\geq 1\%$  and at an incidence higher than placebo, conducted using the recommended dosage regimen**

	Percentage of Patients Reporting Event	
	CHAMPIX N=821	Placebo N=805
<i>Gastrointestinal Disorders</i>		
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
<i>General Disorders and Administration Site Conditions</i>		
Fatigue	4.6	3.9
<i>Metabolism and Nutrition Disorders</i>		
Increased Appetite	1.7	1.2
<i>Nervous System Disorders</i>		
Headache	10.1	8.4
Dizziness	5.2	4.6
Dysgeusia	5.0	3.6
Somnolence	3.0	2.1
<i>Psychiatric Disorders</i>		
Insomnia	13.8	10.6
Abnormal Dreams	12.4	4.5
Sleep Disorder	4.8	2.9

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

**System            Adverse Drug Effects**  
**Organ Class**

**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, 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

## Post-Marketing Experience

The following adverse events have been reported during post-approval use of CHAMPIX. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

There have been reports of neuropsychiatric symptoms such as depressed mood, agitation, hallucinations, changes in behaviour or thinking, anxiety, psychosis, mood swings, aggressive behaviour suicidal ideation and suicide in patients attempting to quit smoking while taking CHAMPIX. Smoking cessation with or without treatment is associated with nicotine withdrawal symptoms and the exacerbation of underlying psychiatric illness. Not all patients had known pre-existing psychiatric illness and not all had discontinued smoking. The role of CHAMPIX in these reports is not known (see **PRECAUTIONS**).

There have also been reports of hypersensitivity reactions, such as angioedema and of rare but severe cutaneous reactions, including Stevens-Johnson Syndrome and Erythema Multiforme in patients taking CHAMPIX (see **PRECAUTIONS**).

There have been reports of myocardial infarction (MI) and cerebrovascular accident (CVA) including ischaemic and haemorrhagic events in patients taking CHAMPIX. In the majority of the reported cases, patients had pre-existing cardiovascular disease and/or other risk factors. Although smoking is a risk factor for MI and CVA, based on temporal relationship between medication use and events, a contributory role of varenicline cannot be ruled out.

## 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, 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 dialyzed 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**

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 wallet.

Aclar / PVC blisters with aluminium foil backing in a pack containing 28 or 56 x 1 mg film-coated tablets in a carton or secondary heat sealed wallet.

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 New Zealand).

Shelf Life: 2 years when stored below 30°C

## **NAME AND ADDRESS OF THE SPONSOR**

Pfizer New Zealand Ltd  
Auckland, New Zealand  
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NEW ZEALAND  
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## **MEDICINE CLASSIFICATION**

Prescription Medicine

CHAMPIX is being monitored on the New Zealand Intensive Medicines Monitoring Program (IMMP).

## **DATE OF PREPARATION**

11 October 2011