Varenicline Tartrate Film Coated Tablets

CHAMPIX®

Pfizer

SAE890

For the use of Registered Medical Practitioners, Hospitals or Laboratories Only

## Varenicline Tartrate Film Coated Tablets

CHAMPIX®

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1. **NAME OF THE MEDICINAL PRODUCT**
CHAMPIX

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**
Each 0.5mg film-coated tablet contains Varenicline tartrate 0.5mg
Each 1mg film-coated tablet contains Varenicline tartrate 1mg
For list of excipients, please see Section 6.1
All strengths/ presentations mentioned in this document may not be available in the market.

3. **PHARMACEUTICAL FORM**
Film-coated tablets.

4. **CLINICAL PARTICULARS**

**4.1 Therapeutic Indications**
Varenicline is indicated for smoking cessation.

**4.2 Posology and Method of Administration**
Smoking cessation therapies are more likely to succeed for patients who are motivated to stop smoking and who are provided with additional advice and support.
The recommended dose of varenicline is 1 mg twice daily following a 1-week titration as follows:

| | |
|---|---|
| Days 1 – 3: | 0.5 mg once daily |
| Days 4 – 7: | 0.5 mg twice daily |
| Day 8 – End of treatment: | 1 mg twice daily |

The patient should set a date to stop smoking. Varenicline dosing should start 1 week before this date.
Patients who cannot tolerate adverse effects of varenicline may have the dose lowered temporarily or permanently.
Varenicline tablets should be swallowed whole with water. Varenicline can be taken with or without food.
Patients should be treated with varenicline for 12 weeks. For patients who have successfully stopped smoking at the end of 12 weeks, an additional course of 12 weeks treatment with varenicline at 1 mg twice daily is recommended. (See section **5.1 Pharmacodynamic Properties** - *Maintenance of Abstinence Study*)
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.
*Patients with Renal Insufficiency:*
No dosage adjustment is necessary for patients with mild (estimated creatinine clearance > 50 ml/min and ≤ 80 ml/min) to moderate (estimated creatinine clearance ≥ 30 ml/min and ≤ 50 ml/min) renal impairment.
For patients with severe renal impairment (estimated creatinine clearance < 30 ml/min), the recommended dose of varenicline is 1 mg once daily. Dosing should begin at 0.5 mg once daily for the first 3 days then increased to 1 mg once daily. There is insufficient clinical experience with varenicline in patients with end stage renal disease. (See section **5.2 Pharmacokinetic Properties** – *Patients with Renal Insufficiency*)
*Patients with Hepatic Impairment:*
No dosage adjustment is necessary for patients with hepatic impairment. (See section **5.2 Pharmacokinetic Properties** – *Patients with Hepatic Impairment*)
*Use in Elderly Patients:*
No dosage adjustment is necessary for elderly patients. Because elderly patients are more likely to have decreased renal function, prescribers should consider the renal status of an elderly patient. (See above *Patients with renal insufficiency* and *section* **5.2 Pharmacokinetic Properties** – *Patients with Renal Insufficiency* and *Use in Elderly Patients*)
*Use in Paediatric Patients:*
Varenicline is not recommended for use in paediatric patients below 18 years of age due to insufficient data on safety and efficacy. (See section **5.2 Pharmacokinetic Properties** – *Use in Paediatric Patients*)

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

**4.4 Special Warnings and Special Precautions for Use**
*Effect of Smoking Cessation:* Physiological changes resulting from smoking cessation, with or without treatment with varenicline, may alter the pharmacokinetics or pharmacodynamics of some medicinal products, for which dosage adjustment may be necessary (examples include theophylline, warfarin and insulin). (See section **4.5 Interaction with Other Medicinal Products and Other Forms of Interaction** – *Warfarin*)
At the end of treatment, discontinuation of varenicline was associated with an increase in irritability, urge to smoke, depression, and/or insomnia in up to 3% of patients.
There have been post-marketing reports of neuropsychiatric symptoms, some serious, including changes in behaviour, or thinking, anxiety, psychosis, mood swings, aggressive behaviour, agitation, depressed mood, suicidal ideation and suicidal behaviour, in patients attempting to quit smoking with varenicline. (See section **4.8 Undesirable Effects**) Physicians should discuss the efficacy and safety profile of varenicline with patients and advise patients attempting to quit smoking with varenicline of the possible emergence of neuropsychiatric symptoms. Patients and families and/or caregivers should be advised that the patient should stop taking varenicline and contact a health care provider 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 varenicline was reported, although in some cases the symptoms persisted; therefore, ongoing follow up should be provided until symptoms resolve. Patients 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 varenicline and the safety and efficacy of varenicline in such patients has not been established. Limited data are available from a single smoking cessation study in patients with stable schizophrenia or schizoaffective disorder (See section **5.1 Pharmacodynamic Properties** - *Study In Subjects with Stable Schizophrenia or Schizoaffective Disorder*).
There have been post-marketing reports of hypersensitivity reactions including angioedema in patients treated with varenicline. Clinical signs included swelling of the face, mouth (tongue, lips, and gums), neck (throat and larynx) and extremities. There were rare reports of life threatening angioedema requiring urgent medical attention due to respiratory compromise. Patients experiencing these symptoms should discontinue treatment with varenicline and contact a health care provider immediately.
There have also been post-marketing reports of rare but severe cutaneous reactions, including Stevens-Johnson Syndrome and Erythema Multiforme in patients using varenicline. As these skin reactions can be life threatening, patients should discontinue treatment at the first sign of rash or skin reaction and contact a healthcare provider immediately.
In a smoking cessation trial of patients with stable cardiovascular disease, while cardiovascular events were infrequent overall, some were reported more frequently in patients treated with varenicline. A meta-analysis of 15 clinical trials, which included the smoking cessation trial of patients with stable cardiovascular disease, had similar results (See section **5.1 Pharmacodynamic Properties** - *Study in Subjects with Cardiovascular Disease*). No causal relationship between these events and varenicline has been established. Smoking is an independent and major risk factor for cardiovascular disease. Patients taking varenicline should be instructed to notify their doctor of new or worsening cardiovascular symptoms and to seek immediate medical attention if they experience signs and symptoms of myocardial infarction or stroke.

**4.5 Interaction with Other Medicinal Products and Other Forms of Interaction**
Based on varenicline characteristics and clinical experience to date, no clinically meaningful drug interactions have been identified. No dosage adjustment of varenicline or co-administered drugs listed below is recommended.
In vitro studies indicate that varenicline is unlikely to alter the pharmacokinetics of compounds that are primarily metabolised by cytochrome P450 enzymes.
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.
In vitro studies demonstrate that active renal secretion of varenicline is mediated by the human organic cation transporter, OCT2. Coadministration with inhibitors of OCT2 does not require a dose adjustment of varenicline as the increase in systemic exposure to varenicline tartrate is not expected to be clinically meaningful (see cimetidine interaction below). Furthermore since metabolism of varenicline represents less than 10% of its clearance, active substances known to affect the cytochrome P450 system are unlikely to alter the pharmacokinetics of varenicline (See section **5.2 Pharmacokinetic Properties** – *Metabolism*) and therefore a dose adjustment of varenicline would not be required.
In vitro studies demonstrate that varenicline does not inhibit human renal transport proteins at therapeutic concentrations. Therefore, medicinal products that are cleared by renal secretion (eg. metformin - see below) are unlikely to be affected by varenicline.
*Metformin:* Varenicline (1 mg twice daily) did not affect the pharmacokinetics of metformin (500 mg twice daily), which is a substrate of OCT2. Metformin had no effect on varenicline pharmacokinetics.
*Cimetidine:* Co-administration of an OCT2 inhibitor, cimetidine (300 mg four times daily), with varenicline (2 mg single dose) increased the systemic exposure of varenicline by 29% due to a reduction in varenicline renal clearance.
*Digoxin:* Varenicline (1 mg twice daily) did not alter the steady-state pharmacokinetics of digoxin administered as a 0.25 mg daily dose.
*Warfarin:* Varenicline (1 mg twice daily) did not alter the pharmacokinetics of a single 25 mg dose of (R, S) warfarin. Prothrombin time (INR) was not affected by varenicline. Smoking cessation itself may result in changes to warfarin pharmacokinetics. (See section **4.4 Special Warnings and Special Precautions for Use** – *Effect of Smoking Cessation*)
*Use with Other Therapies for Smoking Cessation:*
*Bupropion:* Varenicline (1 mg twice daily) did not alter the steady-state pharmacokinetics of bupropion (150 mg twice daily).
*Nicotine replacement therapy (NRT):* When varenicline (1 mg twice daily) and NRT (transdermal 21 mg/day) were co-administered to smokers (N=24) for 12 days, there was a statistically significant decrease in average systolic blood pressure (mean 2.6 mmHg) measured on the final day of the study. In this study, the incidence of nausea, headache, vomiting, dizziness, dyspepsia, and fatigue was greater for the combination than for NRT alone.
Safety and efficacy of varenicline in combination with other smoking cessation therapies have not been studied.

**4.6 Pregnancy and Lactation**
*Pregnancy:*
There are no adequate and well-controlled studies in pregnant women. Varenicline should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (See section **5.3 Preclinical Safety Data**)
*Lactation:*
It is unknown whether varenicline is excreted in human breast milk. Animal studies suggest that varenicline is excreted in breast milk. A decision on whether to discontinue breast-feeding or to discontinue therapy with varenicline should be made taking into account the benefit of breast-feeding to the child and the benefit of varenicline therapy to the woman.

**4.7 Effects on Ability to Drive and Use Machines**
Patients should be advised to use caution driving or operating machinery until they know how quitting smoking and/or varenicline may affect them.

**4.8 Undesirable Effects**
Smoking cessation with or without treatment is associated with various symptoms. For example, dysphoric or depressed mood; insomnia, irritability, frustration or anger; anxiety; difficulty concentrating; restlessness; decreased heart rate; increased appetite or weight gain have been reported in patients attempting to stop smoking. Smoking cessation, with or without pharmacotherapy, has also been associated with the exacerbation of underlying psychiatric illness. No attempt has been made in either the design or the analysis of the varenicline studies to distinguish between adverse events associated with study drug treatment or those possibly associated with nicotine withdrawal.
Clinical trials included approximately 4,000 patients treated with varenicline for up to 1 year (average exposure 84 days). In general, when adverse reactions occurred, onset was in the first week of therapy; severity was generally mild to moderate and there were no differences by age, race or gender with regard to the incidence of adverse reactions.
In patients treated with the recommended dose of 1 mg BID following an initial titration period the adverse event most commonly reported was nausea (28.6%). In the majority of cases nausea occurred early in the treatment period, was mild to moderate in severity and seldom resulted in discontinuation.
The treatment discontinuation rate due to adverse events was 11.4% for varenicline compared with 9.7% for placebo. In this group, the discontinuation rates for the most common adverse events in varenicline treated patients were as follows: nausea (2.7% vs. 0.6% for placebo), headache (0.6% vs. 1.0% for placebo), insomnia (1.3% vs. 1.2% for placebo), and abnormal dreams (0.2% vs. 0.2% for placebo).
All adverse reactions that occurred at an incidence greater than placebo are listed below by system organ class.
**Infections and infestations:** Bronchitis, nasopharyngitis, sinusitis
**Metabolism and nutrition disorders:** Anorexia, decreased appetite, increased appetite, polydipsia
**Psychiatric disorders:** Abnormal dreams, bradyphrenia, insomnia, mood swings, thinking abnormal
**Nervous system disorders:** Circadian rhythm sleep disorder, coordination abnormal, dizziness, dysarthria, dysgeusia, dysphoria, headache, hypoesthesia, hypogeusia, lethargy, libido decreased, restlessness, somnolence, tremor
**Eye disorders:** Eye pain, photophobia, scotoma
**Ear and labyrinth disorders:** Tinnitus
**Cardiac disorders:** Atrial fibrillation, palpitations
**Respiratory, thoracic and mediastinal disorders:** Cough, dyspnoea, hoarseness, postnasal drip, respiratory tract congestion, rhinorrhoea, sinus congestion, snoring, throat irritation
**Gastrointestinal disorders:** Abdominal distension, abdominal pain, aphthous stomatitis, constipation, diarrhoea, dry mouth, dyspepsia, eructation, flatulence, gastritis, gastrooesophageal reflux disease, gingival pain, haematemesis, haematochezia, nausea, stomach discomfort, vomiting
**Skin and subcutaneous tissue disorders:** Acne, erythema, hyperhidrosis, pruritus, rash generalised
**Musculoskeletal and connective tissue disorders:** Joint stiffness, muscle spasms
**Renal and urinary disorders:** Glycosuria, nocturia, polyuria
**Reproductive system and breast disorders:** Menorrhagia, sexual dysfunction
**General disorders and administration site conditions:** Asthenia, chest discomfort, chest pain, fatigue, malaise, pyrexia
**Investigations:** Blood pressure increased, electrocardiogram ST segment depression, electrocardiogram T wave amplitude decreased, heart rate increased, liver function test abnormal, platelet count decreased, weight increased

**4.8.1 Post-Marketing Experience:**
The following adverse events have been reported during post-approval use of varenicline. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
There have been reports of depressed mood, agitation, changes in behaviour or thinking, anxiety, psychosis, mood swings, aggressive behaviour, suicidal ideation and suicide in patients attempting to quit smoking while taking varenicline. Smoking cessation with or without treatment is associated with nicotine withdrawal symptoms and the exacerbation of underlying psychiatric illness. Not all patients in these reports had known pre-existing psychiatric illness and not all had discontinued smoking. The role of varenicline in these reports is not known. (See section **4.4 Special Warnings and Special Precautions for Use**).
There have also been reports of hypersensitivity reactions, such as angioedema and of rare but severe cutaneous reactions, including Stevens-Johnson Syndrome and Erythema Multiforme in patients taking varenicline (See section **4.4 Special Warnings and Special Precautions for Use**).

**4.9 Overdose**
No cases of overdose were reported in pre-marketing clinical trials.
In case of overdose, standard supportive measures should be instituted as required.
Varenicline has been shown to be dialyzed in patients with end stage renal disease, however, there is no experience in dialysis following overdose. (See section **5.2 Pharmacokinetic Properties** – *Patients with Renal Insufficiency*)

5. **PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic Properties**
Varenicline binds with high affinity and selectivity at the $\alpha4\beta2$ neuronal nicotinic acetylcholine receptors, where it acts as a partial agonist - a compound that has both agonist activity, with lower intrinsic efficacy than nicotine, and antagonist activities in the presence of nicotine.
Electrophysiology studies in vitro and neurochemical studies in vivo have shown that varenicline binds to the $\alpha4\beta2$ neuronal nicotinic acetylcholine receptors and stimulates receptor-mediated activity, but at a significantly lower level than nicotine. Nicotine competes for the same human $\alpha4\beta2$ nAChR binding site for which varenicline has higher affinity. Therefore, varenicline can effectively block nicotine's ability to fully activate $\alpha4\beta2$ receptors and the mesolimbic dopamine system, the neuronal mechanism underlying reinforcement and reward experienced upon smoking. Varenicline is highly selective and binds more potently to the $\alpha4\beta2$ receptor subtype ($K_i$=0.15 nM) than to other common nicotinic receptors ($\alpha3\beta4$ $K_i$=84 nM, $\alpha7$ $K_i$= 620 nM, $\alpha1\beta\delta$ $K_i$= 3,400 nM), or to non-nicotinic receptors and transporters ($K_i$ > 1μM, except to 5-HT3 receptors: $K_i$=350 nM).
The efficacy of varenicline in smoking cessation is a result of varenicline's partial agonist activity at the $\alpha4\beta2$ nicotinic receptor where its binding produces an effect sufficient to alleviate symptoms of craving and withdrawal (agonist activity), while simultaneously resulting in a reduction of the rewarding and reinforcing effects of smoking by preventing nicotine binding to $\alpha4\beta2$ receptors (antagonist activity).
*Clinical Efficacy:*
The efficacy of varenicline in smoking cessation was demonstrated in 3 clinical trials involving chronic cigarette smokers (≥ 10 cigarettes per day). 2619 patients received varenicline 1 mg BID (titrated during the first week), 669 patients received bupropion 150 mg BID (also titrated) and 684 patients received placebo.

*Comparative Clinical Studies:*
Two identically designed double-blind clinical trials prospectively compared the efficacy of varenicline (1 mg twice daily), sustained release bupropion (150 mg twice daily) and placebo in smoking cessation. In these 52-week duration studies, patients received treatment for 12 weeks, followed by a 40-week non-treatment phase.

In all studies, patients were provided with an educational booklet on smoking cessation and received up to 10 minutes of smoking cessation counseling at each weekly treatment visit according to Agency for Healthcare Research and Quality guidelines. Patients set a date to stop smoking (target quit date, TQD) with dosing starting 1 week before this date.

The primary endpoint of the two studies was the carbon monoxide (CO) confirmed, 4-week continuous quit rate (4W-CQR) from week 9 through week 12. The primary endpoint for varenicline demonstrated statistical superiority to bupropion and placebo.

After the 40-week non-treatment phase, a key secondary endpoint for both studies was the Continuous Abstinence Rate (CA) at week 52. CA was defined as the proportion of all subjects treated who did not smoke (not even a puff of a cigarette) from week 9 through week 52 and did not have an exhaled CO measurement of > 10 ppm. The 4W-CQR (weeks 9 through 12) and CA rate (weeks 9 through 52) from studies 1 and 2 are included in the following table:

| | Study 1 (n=1022) | | Study 2 (n=1023) | |
|---|---|---|---|---|
| | 4W CQR | CA Wk 9-52 | 4W CQR | CA Wk 9-52 |
| Varenicline | 44.4% | 22.1% | 44.0% | 23.0% |
| Bupropion | 29.5% | 16.4% | 30.0% | 15.0% |
| Placebo | 17.7% | 8.4% | 17.7% | 10.3% |
| Odds ratio Varenicline vs placebo | 3.91 p<0.0001 | 3.13 p<0.0001 | 3.85 p<0.0001 | 2.66 p<0.0001 |
| Odds ratio Varenicline vs bupropion | 1.96 p<0.0001 | 1.45 p=0.0640 | 1.89 p<0.0001 | 1.72 p=0.0062 |

Patient reported craving, withdrawal and reinforcing effects of smoking:
Across both Studies 1 and 2 during active treatment, Patient Reported Outcomes measures demonstrated that craving and withdrawal were significantly reduced in patients randomised to varenicline in comparison with placebo. Varenicline 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 varenicline therapy on the maintenance of abstinence. Patients in this study (n=1,927) received open-label varenicline 1 mg twice daily for 12 weeks. Patients who stopped smoking by Week 12 were then randomised to receive either varenicline (1 mg twice daily) or placebo for an additional 12 weeks for a total study duration of 52 weeks.

The primary study endpoint was the CO-confirmed continuous abstinence rate from week 13 through week 24 in the double-blind treatment phase. A key secondary endpoint was the continuous abstinence (CA) rate for week 13 through week 52.

This study showed the benefit of an additional 12-week treatment with varenicline 1 mg twice daily for the maintenance of smoking cessation compared to placebo. The odds of maintaining abstinence at week 24, following an additional 12 weeks of treatment with varenicline, were 2.47 times those for placebo (p<0.0001). Superiority to placebo for CA was maintained through week 52 (Odds Ratio=1.35, p=0.0126).

The key results are summarised in the following table:

| | Varenicline n=602 | Placebo n=604 | Difference (95% CI) | Odds ratio (95% CI) |
|---|---|---|---|---|
| CA wk 13-24 | 70.6% | 49.8% | 20.8% (15.4%, 26.2%) | 2.47 (1.95, 3.15) |
| CA wk 13-52 | 44.0% | 37.1% | 6.9% (1.4%, 12.5%) | 1.35 (1.07, 1.70) |

Study in Subjects with Cardiovascular Disease:
Varenicline was evaluated in a randomised, double-blind, placebo-controlled study of 703 subjects with stable, documented cardiovascular disease (other than or in addition to hypertension) that had been diagnosed for more than 2 months. Subjects aged 35 to 75 years were randomised to varenicline 1 mg BID or placebo for a treatment of 12 weeks and then were followed for 40 weeks post-treatment. Subjects treated with varenicline had a superior rate of CO-confirmed abstinence during weeks 9 through 12 (47.3 %) compared to subjects treated with placebo (14.3%) (odds ratio 6.05; 95% CI 4.13, 8.86; p<0.0001) and from week 9 through 52 (19.8%) compared to subjects treated with placebo (7.4%) (odds ratio 3.19; 95% CI 1.97, 5.18; p<0.0001). Deaths and serious cardiovascular events occurring over the 52 weeks of the study (treatment-emergent and non-treatment-emergent) were adjudicated by a blinded, independent committee. The following treatment-emergent adjudicated events occurred with a frequency ≥ 1% in either treatment group: nonfatal myocardial infarction (1.1% vs. 0.3% for varenicline and placebo, respectively), and hospitalisation for angina pectoris (0.6% vs. 1.1%). During non-treatment follow up to 52 weeks, adjudicated events with a frequency ≥1% included need for coronary revascularisation (2.0% vs. 0.6%), hospitalisation for angina pectoris (1.7% vs. 1.1%), and new diagnosis of peripheral vascular disease (PVD) or admission for a PVD procedure (1.4% vs. 0.6%). Some of the patients requiring coronary revascularisation underwent the procedure as part of management of nonfatal MI and hospitalisation for angina. Cardiovascular death occurred in 0.3% of patients in the varenicline arm and 0.6% of patients in the placebo arm over the course of the 52 week study.

The key results are summarised in the following table:

| | Varenicline n=353 | Placebo n=350 | Odds ratio (95% CI), p value |
|---|---|---|---|
| CA wk 9-12 | 47.3% | 14.3% | 6.05 (4.13, 8.86) p<0.0001 |
| CA wk 9-52 | 19.8% | 7.4% | 3.19 (1.97, 5.18) p<0.0001 |

A meta-analysis of 15 clinical trials of ≥ 12 weeks treatment duration, including 7002 patients (4190 varenicline, 2812 placebo), was conducted to systematically assess the cardiovascular safety of varenicline. The study in patients with stable cardiovascular disease described above was included in the meta-analysis.

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

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

Study in Subjects with Chronic Obstructive Pulmonary Disease:
Varenicline was evaluated in a randomised, double-blind, placebo-controlled study of 499 subjects with mild-to-moderate Chronic Obstructive Pulmonary Disease with post-bronchodilator FEV1/FVC <70% and FEV1 ≥ 50% of predicted normal value. Subjects aged ≥ 35 years were randomised to varenicline 1 mg BID or placebo for a treatment of 12 weeks and then were followed for 40 weeks post-treatment. Subjects treated with varenicline had a superior rate of CO-confirmed abstinence during weeks 9 through 12 (42.3%) compared to subjects treated with placebo (8.8%) (odds ratio 8.40; 95% CI 4.99, 14.14; p<0.0001) and from week 9 through 52 (18.6%) compared to subjects treated with placebo (5.6%) (odds ratio 4.04; 95% CI 2.13, 7.67; p<0.0001). Adverse events in this study were quantitatively and qualitatively similar to those observed in premarketing studies.

The key results are summarised in the following table:

| | Varenicline n=248 | Placebo n=251 | Odds ratio (95% CI), p value |
|---|---|---|---|
| CA wk 9-12 | 42.3% | 8.8% | 8.40 (4.99, 14.14) p<0.0001 |
| CA wk 9-52 | 18.6% | 5.6% | 4.04 (2.13, 7.67) p<0.0001 |

Study in Subjects with Stable Schizophrenia or Schizoaffective Disorder:
Varenicline safety and tolerability was assessed in a double-blind study of 128 smokers with stable schizophrenia or schizoaffective disorder, on antipsychotic medication, randomised 2:1 to varenicline (1 mg twice daily) or placebo for 12 weeks with 12-week non-drug follow-up.

The most common adverse events in subjects taking varenicline were nausea (23.8% vs. 14.0% on placebo), headache (10.7% vs. 18.6% on placebo) and vomiting (10.7% vs. 9.3% on placebo). Among reported neuropsychiatric adverse events, insomnia was the only event reported in either treatment group in ≥ 5% of subjects at a rate higher in the varenicline group than in placebo (9.5% vs. 4.7%).

Overall, there was no worsening of schizophrenia in either treatment group as measured by psychiatric scales and there were no overall changes in extra-pyramidal signs.

In the varenicline group compared to placebo, a higher proportion of subjects reported suicidal ideation or behaviour prior to enrollment (lifetime history) and after the end of active treatment period (on Days 33 to 85 after the last dose of drugs). During the active treatment period, the incidence of suicide-related events was similar between the varenicline-treated and the placebo-treated subjects (11 vs. 9.3 %, respectively). The percentage of subjects with suicide-related events in the active treatment phase compared to post-treatment phase was unchanged in the varenicline group; in the placebo group, this percentage was lower in the post-treatment phase. There were no completed suicides. There was one suicidal attempt in a varenicline-treated subject whose lifetime history included several similar attempts. The limited data available from this single smoking cessation study is not sufficient to allow definitive conclusions to be drawn. However, these data do not suggest that varenicline treatment causes or worsens suicidality in subjects with stable schizophrenia or schizoaffective disorder.

**5.2 Pharmacokinetic Properties**

*Absorption:*
Maximum plasma concentrations of varenicline occur typically within 3-4 hours after oral administration. Following administration of multiple oral doses to healthy volunteers, steady-state conditions were reached within 4 days. Absorption is virtually complete after oral administration and systemic availability is high. Oral bioavailability of varenicline is unaffected by food or time-of-day dosing.

*Distribution:*
Varenicline distributes into tissues, including the brain. Apparent volume of distribution averaged 415 liters (%CV= 50) at steady state. Plasma protein binding of varenicline is low (≤ 20%) and independent of both age and renal function.

*Metabolism:*
Varenicline undergoes minimal metabolism with 92% excreted unchanged in the urine and less than 10% excreted as metabolites. Minor metabolites in urine include varenicline N-carbamoylglucuronide and hydroxyvarenicline. In circulation, varenicline comprises 91% of drug-related material. Minor circulating metabolites include varenicline N-carbamoylglucuronide and N-glucosylvarenicline.

*Excretion:*
The elimination half-life of varenicline is approximately 24 hours. Renal elimination of varenicline is primarily through glomerular filtration along with active tubular secretion via the organic cationic transporter, OCT2.

*Linearity/Non Linearity:*
Varenicline exhibits linear kinetics when given as single (0.1 to 3 mg) or repeated (1 to 3 mg/day) doses.

*Pharmacokinetics in Special Patient Populations:*
There are no clinically meaningful differences in varenicline pharmacokinetics due to age, race, gender, smoking status, or use of concomitant medications, as demonstrated in specific pharmacokinetic studies and in population pharmacokinetic analyses.

*Patients with Hepatic Impairment:*
Due to the absence of significant hepatic metabolism, varenicline pharmacokinetics should be unaffected in patients with hepatic impairment. (See section **4.2 Posology and Method of Administration** – *Patients with Hepatic Impairment*)

*Patients with Renal Insufficiency:*
Varenicline pharmacokinetics were unchanged in subjects with mild renal impairment (estimated creatinine clearance > 50 ml/min and ≤ 80 ml/min). In patients with moderate renal impairment (estimated creatinine clearance ≥ 30 ml/min and ≤ 50 ml/min), varenicline exposure increased 1.5-fold compared with subjects with normal renal function (estimated creatinine clearance > 80 ml/min). In subjects with severe renal impairment (estimated creatinine clearance < 30 ml/min), varenicline exposure was increased 2.1-fold. In subjects with end-stage-renal disease (ESRD), varenicline was efficiently removed by hemodialysis. (See section **4.2 Posology and Method of Administration** - *Patients with Renal Insufficiency*)

*Use in Elderly Patients:*
The pharmacokinetics of varenicline in elderly patients with normal renal function (aged 65-75 years) is similar to that of younger adult subjects. In elderly patients with severe renal impairment, dosage adjustment is recommended. (See section **4.2 Posology and Method of Administration** – *Patients with Renal Insufficiency*)

*Use in Paediatric Patients:*
When 22 paediatric patients 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. (See section **4.2 Posology and Method of Administration** – *Use in Paediatric Patients*)

**5.3 Preclinical Safety Data**

**Carcinogenesis, Mutagenesis, Impairment of Fertility**
Lifetime carcinogenicity studies were performed in CD-1 mice and Sprague-Dawley rats. There was no evidence of a carcinogenic effect in mice administered varenicline by oral gavage for 2 years at doses up to 20 mg/kg/day (47 times the maximum recommended human daily exposure based on AUC). Rats were administered varenicline (1, 5, and 15 mg/kg/day) by oral gavage for 2 years. In male rats (n = 65 per sex per dose group), incidences of hibernoma (tumor of the brown fat) were increased at the mid dose (1 tumor, 5 mg/kg/day, 23 times the maximum recommended human daily exposure based on AUC) and maximum dose (2 tumors, 15 mg/kg/day, 67 times the maximum recommended human daily exposure based on AUC). The clinical relevance of this finding to humans has not been established. There was no evidence of carcinogenicity in female rats.

Varenicline was not genotoxic, with or without metabolic activation, in the following assays: Ames bacterial mutation assay; mammalian CHO/HGPRT assay; and tests for cytogenetic aberrations in vivo in rat bone marrow and in vitro in human lymphocytes.

There was no evidence of impairment of fertility in either male or female Sprague-Dawley rats administered varenicline succinate up to 15 mg/kg/day (67 and 36 times, respectively, the maximum recommended human daily exposure based on AUC at 1 mg BID). However, a decrease in fertility was noted in the offspring of pregnant rats who were administered varenicline succinate at an oral dose of 15 mg/kg/day (36 times the maximum recommended human daily exposure based on AUC at 1 mg BID). This decrease in fertility in the offspring of treated female rats was not evident at an oral dose of 3 mg/kg/day (9 times the maximum recommended human daily exposure based on AUC at 1 mg BID).

**Teratogenesis**
Varenicline succinate was not teratogenic in rats and rabbits at oral doses up to 15 and 30 mg/kg/day, respectively (36 and 50-times the maximum recommended human daily exposure based on AUC at 1 mg BID, respectively).

**Nonteratogenic Effects**
Varenicline succinate has been shown to have an adverse effect on the foetus in animal reproduction studies. Administration of varenicline succinate to pregnant rabbits resulted in reduced foetal weights at an oral dose of 30 mg/kg/day (50 times the human AUC at 1 mg BID); this reduction was not evident following treatment with 10 mg/kg/day (23 times the maximum recommended daily human exposure based on AUC). In addition, in the offspring of pregnant rats treated with varenicline succinate there were decreases in fertility and increases in auditory startle response at an oral dose of 15 mg/kg/day (36 times the maximum recommended human daily exposure based on AUC at 1 mg BID).

Nonclinical data indicate varenicline has reinforcing properties albeit with lower potency than nicotine. Moreover, in clinical studies in humans, varenicline showed low abuse potential.

## 6. PHARMACEUTICAL PARTICULARS

**6.1 List of Excipients**

Core Tablet
Cellulose, microcrystalline
Calcium Hydrogen Phosphate, Anhydrous
Croscarmellose Sodium
Silica, Colloidal Anhydrous
Magnesium Stearate

Film Coating
Hypromellose
Titanium Dioxide (E171)
Macrogols
Triacetin

Champix 1 mg tablets: additionally contains Indigo Carmine Aluminium Lake (E132) in the film coating.

**6.2 Incompatibilities**
Not Applicable.

**6.3 Shelf Life**
Refer to Pack. Refer the outer carton for the date of expiry. The date of expiry is the last day of the month.

**6.4 Special Precautions for Storage**
Store below 30°C.

**6.5 Nature and Contents of Container**
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.
Aclar / PVC / blisters with aluminium foil backing containing 28 x 1 mg film coated tablets.

**6.6 Instructions for Use and Handling**
No special requirements.

Please refer to the current Package Insert for updated information.
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