Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Varenicline Ascend 1 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

Light blue, capsular biconvex, film coated tablets, debossed with 'VC' on one side and '1' on other side (length: 10.25 ± 0.2 mm, width: 5.24 ± 0.2 mm, thickness: 3.39 ± 0.3 mm).

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Varenicline Ascend is indicated for smoking cessation in adults.

4.2 Posology and method of administration

Posology

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

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

The patient should set a date to stop smoking. Varenicline Ascend dosing should usually start at 1-2 weeks before this date (see section 5.1). Patients should be treated with Varenicline Ascend e 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 Ascend at 1 mg twice daily may be considered for the maintenance of abstinence (see section 5.1).

A gradual approach to quitting smoking with Varenicline Ascend should be considered for patients who are not able or willing to quit abruptly. Patients should reduce smoking during the first 12 weeks of treatment and quit by the end of that treatment period. Patients should then continue taking Varenicline Ascend for an additional 12 weeks for a total of 24 weeks of treatment (see section 5.1).

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

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

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

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

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

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

For patients with severe renal impairment (estimated creatinine clearance < 30 ml/min), the recommended dose of Varenicline Ascend is 1 mg once daily. Dosing should begin at 0.5 mg once daily for the first 3 days then increased to 1 mg once daily. Based on insufficient clinical experience with Varenicline Ascend in patients with end stage renal disease, treatment is not recommended in this patient population (see section 5.2).

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

Paediatric population
Varenicline Ascend is not recommended for use in paediatric patients because its efficacy in this population was not demonstrated (see sections 5.1 and 5.2).

Method of administration

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Effect of smoking cessation

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

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

A large randomised, double-blind, active and placebo-controlled study was conducted to compare the risk of serious neuropsychiatric events in patients with and without a history of psychiatric disorder treated for smoking cessation with varenicline, bupropion, nicotine replacement therapy patch (NRT) or placebo. The primary safety endpoint was a composite of neuropsychiatric adverse events that have been reported in post-marketing experience.

The use of varenicline in patients with or without a history of psychiatric disorder was not associated with an increased risk of serious neuropsychiatric adverse events in the composite primary endpoint compared with placebo (see section 5.1 Pharmacodynamic properties - Study in Subjects with and without a History of Psychiatric Disorder).

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

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

History of psychiatric disorders

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

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

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

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

Seizures

In clinical trials and post-marketing experience there have been reports of seizures in patients with or without a history of seizures, treated with Varenicline. Varenicline should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold.

Treatment discontinuation

At the end of treatment, discontinuation of Varenicline was associated with an increase in irritability, urge to smoke, depression, and/or insomnia in up to 3% of patients. The prescriber should inform the patient accordingly and discuss or consider the need for dose tapering.

Cardiovascular events

Patients taking 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 (see section 5.1).

Hypersensitivity reactions

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

Cutaneous reactions

There have also been post-marketing reports of rare but severe cutaneous reactions, including Stevens - Johnson syndrome and Erythema Multiforme in patients using varenicline. As these skin reactions can be life threatening, patients should discontinue treatment at the first sign of rash or skin reaction and contact a healthcare provider immediately.

Excipient information

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

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

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

Furthermore since metabolism of varenicline represents less than 10% of its clearance, active substances known to affect the cytochrome P450 system are unlikely to alter the pharmacokinetics of varenicline (see section 5.2) and therefore a dose adjustment of Varenicline would not be required.

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

Metformin

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

Cimetidine

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

Digoxin

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

Warfarin

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

Alcohol

There are limited clinical data on any potential interaction between alcohol and varenicline. There have been post marketing reports of increased intoxicating effects of alcohol in patients treated with varenicline. A causal relationship between these events and varenicline use has not been established.

Use with other therapies for smoking cessation

Bupropion
Varenicline did not alter the steady-state pharmacokinetics of bupropion.

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

Safety and efficacy of Varenicline in combination with other smoking cessation therapies have not been studied.

4.6 Fertility, pregnancy and lactation

Pregnancy

A moderate amount of data on pregnant women indicated no malformative or foetal/neonatal toxicity of varenicline (see section 5.1).

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

Breast-feeding

It is unknown whether varenicline is excreted in human breast milk. Animal studies suggest that varenicline is excreted in breast milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Varenicline should be made taking into account the benefit of breast-feeding to the child and the benefit of Varenicline therapy to the woman.

Fertility

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

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

Smoking cessation with or without treatment is associated with various symptoms. For example, dysphoric or depressed mood; insomnia, irritability, frustration or anger; anxiety; difficulty concentrating; restlessness; decreased heart rate; increased appetite or weight gain have been reported in patients attempting to stop smoking. No attempt has been made in either the design or the analysis of the varenicline studies to distinguish between adverse reactions associated with study drug treatment or those possibly associated with nicotine withdrawal. Adverse drug reactions are based on evaluation of data from pre-marketing phase 2-3 studies and updated based on pooled data from 18 placebo-controlled pre- and post-marketing studies, including approximately 5,000 patients treated with varenicline.

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

Tabulated summary of adverse reactions

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

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

Common	Somnolence, dizziness, dysgeusia
Uncommon	Seizure, tremor, lethargy, hypoaesthesia
Rare	Cerebrovascular accident, hypertonia, dysarthria, coordination abnormal, hypogeusia, circadian rhythm sleep disorder
Not known	Transient loss of consciousness
Eye disorders	
Uncommon	Conjunctivitis, eye pain
Rare	Scotoma, scleral discolouration, mydriasis, photophobia, myopia, lacrimation increased
Ear and labyrinth disorders	
Uncommon	Tinnitus
Cardiac disorders	
Uncommon	Myocardial infarction, angina pectoris, tachycardia, palpitations, heart rate increased
Rare	Atrial fibrillation, electrocardiogram ST segment depression, electrocardiogram T wave amplitude decreased
Vascular disorders	
Uncommon	Blood pressure increased, hot flush
Respiratory, thoracic and mediastinal disorders	
Common	Dyspnoea, cough
Uncommon	Upper respiratory tract inflammation, respiratory tract congestion, dysphonia, rhinitis allergic, throat irritation, sinus congestion, upperairway cough syndrome, rhinorrhoea
Rare	Laryngeal pain, snoring
Gastrointestinal disorders	
Very common	Nausea
Common	Gastrooesophageal reflux disease, vomiting, constipation, diarrhoea, abdominal distension, abdominal pain, toothache, dyspepsia, flatulence, dry mouth
Uncommon	Haematochezia, gastritis, change of bowel habit, eructation, aphthous stomatitis, gingival pain
Rare	Haematemesis, abnormal faeces, tongue coated
Skin and subcutaneous tissue disorders	
Common	Rash, pruritus
Uncommon	Erythema, acne, hyperhidrosis, night sweats
Rare	Severe cutaneous reactions, including Stevens Johnson Syndrome and Erythema Multiforme, angioedema
Musculoskeletal and connective tissue disorders	
Common	Arthralgia, myalgia, back pain
Uncommon	Muscle spasms, musculoskeletal chest pain
Rare	Joint stiffness, costochondritis
Renal and urinary disorders	
Uncommon	Pollakiuria, nocturia
Rare	Glycosuria, polyuria
Reproductive system and breast disorders	
Uncommon	Menorrhagia
Rare	Vaginal discharge, sexual dysfunction
General disorders and administration site conditions	
Common	Chest pain, fatigue
Uncommon	Chest discomfort, influenza like illness, pyrexia, asthenia, malaise
Rare	Feeling cold, cyst
Investigations	
Common	Liver function test abnormal
Rare	Semen analysis abnormal, C-reactive protein increased, blood calcium Decreased
* Frequencies are estimated from a post-marketing, observational cohort study	

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

No cases of overdose were reported in pre-marketing clinical trials.

In case of overdose, standard supportive measures should be instituted as required.

Varenicline has been shown to be dialyzed in patients with end stage renal disease (see section 5.2), however, there is no experience in dialysis following overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

Varenicline binds with high affinity and selectivity at the α4β2 neuronal nicotinic acetylcholine receptors, where it acts as a partial agonist - a compound that has both agonist activity, with lower intrinsic efficacy than nicotine, and antagonist activities in the presence of nicotine.

Electrophysiology studies in vitro and neurochemical studies in vivo have shown that varenicline binds to the α4β2 neuronal nicotinic acetylcholine receptors and stimulates receptor-mediated activity, but at a significantly lower level than nicotine. Nicotine competes for the same human α4β2 nAChR binding site for which varenicline has higher affinity. Therefore, varenicline can effectively block nicotine's ability to fully activate α4β2 receptors and the mesolimbic dopamine system, the neuronal mechanism underlying reinforcement and reward experienced upon smoking. Varenicline is highly selective and binds more potently to the α4β2 receptor subtype (Ki=0.15 nM) than to other common nicotinic receptors (α3β4 Ki=84 nM, α7 Ki= 620 nM, α1βγδ Ki= 3,400 nM), or to non-nicotinic receptors and transporters (Ki > 1μM, except to 5-HT3 receptors: Ki=350 nM).

Pharmacodynamic effects

The efficacy of Varenicline in smoking cessation is a result of varenicline's partial agonist activity at the α4β2 nicotinic receptor where its binding produces an effect sufficient to alleviate symptoms of craving and withdrawal (agonist activity), while simultaneously resulting in a reduction of the rewarding and reinforcing effects of smoking by preventing nicotine binding to α4β2 receptors(antagonist activity).

Clinical efficacy and safety

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

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

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, 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; superiority to placebo for CA was maintained through week 52. The key results are summarised in the following table:

Continuous Abstinence Rates in Subjects Treated with Varenicline versus Placebo

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

*CA: Continuous Abstinence Rate

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

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

Study in subjects re-treated with Varenicline
Varenicline was evaluated in a double-blind, placebo-controlled trial of 494 patients who had made a previous attempt to quit smoking with Varenicline, and either did not succeed in quitting or relapsed after treatment. Subjects who experienced an

adverse event of a concern during previous treatment were excluded. Subjects were randomised 1:1 to Varenicline 1 mg twice daily (N=249) or placebo (N=245) for 12 weeks of treatment and followed for up to 40 weeks post-treatment. Patients included in this study had taken Varenicline for a smoking-cessation attempt in the past (for a total treatment duration of a minimum of two weeks), at least three months prior to study entry, and had been smoking for at least four weeks.

Patients treated with Varenicline had a superior rate of CO-confirmed abstinence during weeks 9 through 12 and from weeks 9 through 52 compared to subjects treated with placebo. The key results are summarised in the following table:

Continuous Abstinence Rates in Subjects Treated with Varenicline versus Placebo

	VARENICLINE n=249	Placebo n=245	Odds ratio (95% CI), p value
CA* wk 9-12	45.0%	11.8%	7.08 (4.34, 11.55), p<0.0001
CA* wk 9-52	20.1%	3.3%	9.00 (3.97, 20.41), p<0.0001
*CA: Continuous Abstinence			

Gradual approach to quitting smoking
Varenicline was evaluated in a 52-week double-blind placebo-controlled study of 1,510 subjects who were not able or willing to quit smoking within four weeks, but were willing to gradually reduce their smoking over a 12 week period before quitting. Subjects were randomised to either varenicline 1 mg twice daily (n=760) or placebo (n=750) for 24 weeks and followed up post -treatment through week 52. Subjects were instructed to reduce the number of cigarettes smoked by at least 50 percent by the end of the first four weeks of treatment, followed by a further 50 percent reduction from week four to week eight of treatment, with the goal of reaching complete abstinence by 12 weeks. After the initial 12-week reduction phase, subjects continued treatment for another 12 weeks. Subjects treated with Varenicline had a significantly higher Continuous Abstinence Rate compared with placebo; the key results are summarised in the following table:

Continuous Abstinence Rates in Subjects Treated with Varenicline versus Placebo

	VARENICLINE n=760	Placebo n=750	Odds ratio (95% CI), p value
CA* wk 15-24	32.1%	6.9%	8.74 (6.09, 12.53), p<0.0001
CA* wk 21-52	27.0%	9.9%	4.02 (2.94, 5.50), p<0.0001
*CA: Continuous Abstinence Rate			

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

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

Deaths and serious cardiovascular events were adjudicated by a blinded, committee. The following adjudicated events occurred with a frequency ≥ 1% in either treatment group during treatment (or in the 30-day period after treatment): nonfatal myocardial infarction (1.1% vs. 0.3% for Varenicline and placebo, respectively), and hospitalisation for angina pectoris (0.6% vs. 1.1%). During non-treatment follow up to 52 weeks, the adjudicated events included need for coronary revascularisation (2.0% vs. 0.6%), hospitalisation for angina pectoris (1.7% vs. 1.1%), and new diagnosis of peripheral vascular disease (PVD) or admission for a PVD procedure (1.4% vs. 0.6%). Some of the patients requiring coronary revascularisation underwent the procedure as part of management of nonfatal MI and hospitalisation for angina. Cardiovascular death occurred in 0.3% of patients in the Varenicline arm and 0.6% of patients in the placebo arm over the course of the 52-week study.

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

Cardiovascular safety assessment study in subjects with and without a history of psychiatric disorder
The cardiovascular (CV) safety of VARENICLINE was evaluated in the Study in Subjects with and without a History of Psychiatric Disorder (parent study; see section 5.1 - Neuropsychiatric safety) and its nontreatment extension, the Cardiovascular Safety Assessment Study, which enrolled 4595 of the 6293 subjects who completed the parent study (N=8058) and followed them through week 52. Of all subjects treated in the parent study, 1749 (21.7%) had a medium CV risk and 644 (8.0%) had a high CV risk, as defined by Framingham score.

The primary CV endpoint was the time to major adverse cardiovascular events (MACE), defined as cardiovascular death, non-fatal myocardial infarction or non-fatal stroke during treatment. Deaths and cardiovascular events were adjudicated by a blinded, independent committee.

The following table shows the incidence of MACE and Hazard Ratios vs placebo for all treatment groups during treatment, and cumulative for treatment plus 30 days and through end of study.

	VARENICLINE N=2016	**Bupropion N=2006**	**NRT N=2022**	**Placebo N=2014**
During treatment				
MACE, n (%)	1 (0.05)	2 (0.10)	1 (0.05)	4 (0.20)
Hazard Ratio(95%CI)vs placebo	0.29 (0.05, 1.68)	0.50 (0.10, 2.50)	0.29 (0.05, 1.70)	
During treatment plus 30 days				
MACE, n (%)	1 (0.05)	2 (0.10)	2 (0.10)	4 (0.20)
Hazard Ratio(95%CI)vs placebo	0.29 (0.05, 1.70)	0.51 (0.10, 2.51)	0.50 (0.10, 2.48)	
Through end of study				
MACE, n (%)	3 (0.15)	9 (0.45)	6 (0.30)	8 (0.40)
Hazard Ratio(95%CI)vs placebo	0.39 (0.12, 1.27)	1.09 (0.42, 2.83)	0.75 (0.26, 2.13)	

The use of Varenicline, bupropion, and NRT was not associated with an increased risk of CV AEs in smokers treated for up to 12 weeks and followed for up to 1 year compared to placebo, although because of the relatively low number of events overall, an association cannot be entirely ruled out.

Subjects with mild-moderate chronic obstructive pulmonary disease (COPD)

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

	4WCQR	**CAWk9-52**
VARENICLINE, (n = 248)	42.3%	18.5%
Placebo, (n = 251)	8.8%	5.6%
Odds ratio (VARENICLINE vs. Placebo)	8.40 p < 0.0001	4.04 p < 0.0001

Study in subjects with a history of major depressive disorder

The efficacy of varenicline was confirmed in a randomised placebo-controlled trial in 525 subjects with a history of major depression in the past two years or under current stable treatment. The cessation rates in this population were similar to those reported in the general population. Continuous abstinence rate between weeks 9-12 was 35.9% in the varenicline treatment group versus 15.6% in the placebo group (OR 3.35 (95% CI 2.16-5.21)) and between weeks 9-52 was 20.3% versus 10.4% respectively (OR 2.36 (95% CI 1.40-3.98)). The most common adverse events (≥ 10%) in subjects taking varenicline were nausea (27.0% vs. 10.4% on placebo), headache (16.8% vs. 11.2%), abnormal dreams (11.3% vs. 8.2%), insomnia (10.9% vs. 4.8%) and irritability (10.9% vs. 8.2%). Psychiatric scales showed no differences between the varenicline and placebo groups and no overall worsening of depression, or other psychiatric symptoms, during the study in either treatment group.

Study in subjects with stable schizophrenia or schizoaffective disorder

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

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

Overall, there was no worsening of schizophrenia in either treatment group as measured by psychiatric scales and there were no overall changes in extra-pyramidal signs. In the varenicline group compared to placebo, a higher proportion of subjects reported suicidal ideation or behaviour prior to enrolment (lifetime history) and after the end of active treatment period (on Days 33 to 85 after the last dose of treatment). During the active treatment period, the incidence of suicide-related events was similar between the varenicline-treated and the placebo-treated subjects (11 vs. 9.3%, respectively). The percentage of subjects with suicide-related events in the active treatment phase compared to post-treatment phase was unchanged in the varenicline group; in the placebo group, this percentage was lower in the post-treatment phase. Although there were no completed suicides, there was one suicidal attempt in a varenicline-treated subject whose lifetime history included several similar attempts. The limited data available from this single smoking cessation study are not sufficient to allow for definitive conclusions to be drawn about the safety in patients with schizophrenia or schizoaffective disorder.

Neuropsychiatric safety Study in Subjects with and without a History of Psychiatric Disorder: Varenicline was evaluated in a randomised, double-blind, active and placebo-controlled study that included subjects with a history of psychiatric disorder (psychiatric cohort, N=4074) and subjects without a history of psychiatric disorder (non-psychiatric cohort, N=3984). Subjects aged 18-75 years, smoking 10 or more cigarettes per day were randomised 1:1:1:1 to varenicline 1 mg BID, bupropion SR 150 mg BID, nicotine replacement therapy patch (NRT) 21 mg/day with taper or placebo for a treatment period of 12 weeks; they were then followed for another 12 weeks post-treatment.

The primary safety endpoint was a composite of the following neuropsychiatric (NPS) adverse events: severe events of anxiety, depression, feeling abnormal, or hostility, and/or moderate or severe events of agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal ideation, suicidal behaviour or completed suicide.

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

In addition, the table shows the subset of the composite NPS AE endpoint of severe intensity:

	Non-psychiatric Cohort N=3984			
	Varenicline	**Bupropion**	**NRT**	**Placebo**
Number of Patients Treated	990	989	1006	999
Composite NPS AE Primary End point, n(%)	13 (1.3)	22 (2.2)	25 (2.5)	24 (2.4)
RD(95%CI) vs Placebo	-1.28 (-2.40, -0.15)	-0.08 (-1.37, 1.21)	-0.21 (-1.54,1.12)	
Composite NPS AE Endpoint of severe intensity n(%)	1 (0.1)	4 (0.4)	3 (0.3)	5 (0.5)

AE, adverse event; NRT=Nicotine replacement therapy patch

The rates of events in the composite endpoint were low across all treatment groups and were similar or lower for each of the active treatments compared to placebo. The use of varenicline, bupropion and NRT in the non-psychiatric cohort was not associated with a significantly increased risk of NPS adverse events in the composite primary endpoint compared with placebo (95% CIs were lower than or included zero).

The percentage of subjects with suicidal ideation and/or behaviour based on the Columbia-Suicide Severity Rating Scale (C-SSRS) was similar between the varenicline and placebo groups during treatment and in the non- treatment follow-up, as shown in the following table:

	Non-psychiatric Cohort N=3984			
	Varenicline N=990 n(%)	**Bupropion N=989 n(%)**	**NRT N=1006 n(%)**	**Placebo N=999 n(%)**
During treatment				
Number assessed	988	983	996	995
Suicidal behaviour and/or ideation	7 (0.7)	4 (0.4)	3 (0.3)	7 (0.7)
Suicidal behaviour	0	0	1 (0.1)	1 (0.1)
Suicidal ideation	7 (0.7)	4 (0.4)	3 (0.3)	6 (0.6)
During follow up				
Number assessed	807	816	800	805
Suicidal behaviour and/or ideation	3 (0.4)	2 (0.2)	3 (0.4)	4 (0.5)
Suicidal behaviour	0	1 (0.1)	0	0
Suicidal ideation	3 (0.4)	2 (0.2)	3 (0.4)	4 (0.5)

NRT=Nicotine replacement therapy patch

There was one completed suicide, which occurred during treatment in a subject treated with placebo in the non-psychiatric cohort.

The following table shows the rates of the composite NPS adverse event primary endpoint by treatment group and the RDs (95% CI) vs placebo in the psychiatric cohort. The individual components of the endpoint are also shown.

In addition, the table shows the subset of the composite NPS AE endpoint of severe intensity:

	Psychiatric Cohort N=4074			
	Varenicline	**Bupropion**	**NRT**	**Placebo**
Number of Patients Treated	1026	1017	1016	1015
Composite NPS AE Primary Endpoint,n(%)	67 (6.5)	68 (6.7)	53 (5.2)	50 (4.9)
RD (95% CI) vs Placebo	1.59 (-0.42, 3.59)	1.78 (-0.24, 3.81)	0.37 (-1.53, 2.26)	
NPS AE Primary Endpoint Components n (%):				
Anxiety[a]	5 (0.5)	4 (0.4)	6 (0.6)	2 (0.2)
Depression[a]	6 (0.6)	4 (0.4)	7 (0.7)	6 (0.6)
Feeling abnormal[a]	0	1 (0.1)	0	0
Hostility[a]	0	0	0	0
Agitation[b]	25 (2.4)	29 (2.9)	21 (2.1)	22 (2.2)
Aggression[b]	14 (1.4)	9 (0.9)	7 (0.7)	8 (0.8)
Delusions[b]	1 (0.1)	1 (0.1)	1 (0.1)	0
Hallucinations[b]	5 (0.5)	4 (0.4)	2 (0.2)	2 (0.2)
Homicidal ideation[b]	0	0	0	0
Mania[b]	7 (0.7)	9 (0.9)	3 (0.3)	6 (0.6)
Panic[b]	7 (0.7)	16 (1.6)	13 (1.3)	7 (0.7)
Paranoia[b]	1 (0.1)	0	0	2 (0.2)
Psychosis[b]	4 (0.4)	2 (0.2)	3 (0.3)	1 (0.1)
Suicidal behaviour[b]	1 (0.1)	1 (0.1)	0	1 (0.1)
Suicidal ideation[b]	5 (0.5)	2 (0.2)	3 (0.3)	2 (0.2)
Completed suicide[b]				

	0	0	0	0
Composite NPS AE Endpoint of severe intensity n (%)	14 (1.4)	14 (1.4)	14 (1.4)	13 (1.3)

AE, adverse event; aGrade = severe intensity AE; bGrade = moderate and severe intensity AE; NRT=Nicotine replacement therapy patch

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

In the psychiatric cohort, the percentage of subjects with suicidal ideation and/or behaviour based on the Columbia-Suicide Severity Rating Scale (C-SSRS) was similar between the varenicline and placebo groups during treatment and in the non-treatment follow-up, as shown in the following table:

	Psychiatric Cohort N=4074			
	Varenicline N=1026 n(%)	**Bupropion N=1017 n(%)**	**NRT N=1016 n(%)**	**Placebo N=1015 n(%)**
During treatment				
Number assessed	1017	1012	1006	1006
Suicidal behaviour and/or ideation	27 (2.7)	15 (1.5)	20 (2.0)	25 (2.5)
Suicidal behaviour	0	1 (0.1)	0	2 (0.2)
Suicidal ideation	27 (2.7)	15 (1.5)	20 (2.0)	25 (2.5)
During follow up				
Number assessed	833	836	824	791
Suicidal behaviour and/or ideation	14 (1.7)	4 (0.5)	9 (1.1)	11 (1.4)
Suicidal behaviour	1 (0.1)	0	1 (0.1)	1 (0.1)
Suicidal ideation	14 (1.7)	4 (0.5)	9 (1.1)	11 (1.4)

NRT=Nicotine replacement therapy patch

There were no completed suicides reported in the psychiatric cohort.

The most commonly reported adverse events in subjects treated with varenicline in this study were similar to those observed in premarketing studies.

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

The key efficacy results are summarised in the following table:

	Non-psychiatric Cohort	**Psychiatric Cohort**
CA9-12n/N (%)		
Varenicline	382/1005 (38.0%)	301/1032 (29.2%)
Bupropion	261/1001 (26.1%)	199/1033 (19.3%)
NRT	267/1013 (26.4%)	209/1025 (20.4%)
Placebo	138/1009 (13.7%)	117/1026 (11.4%)
Treatment Comparisons: Odds ratio (95% CI), p value		
Varenicline vs Placebo	4.00 (3.20, 5.00), P<0.0001	3.24 (2.56, 4.11), P<0.0001
Bupropion vs Placebo	2.26 (1.80, 2.85), P<0.0001	1.87 (1.46, 2.39), P<0.0001
NRT vs Placebo	2.30 (1.83, 2.90), P<0.0001	2.00 (1.56, 2.55), P<0.0001
Varenicline vs Bupropion	1.77 (1.46, 2.14), P<0.0001	1.74 (1.41, 2.14), P<0.0001
Varenicline vs NRT	1.74 (1.43, 2.10), P<0.0001	1.62 (1.32, 1.99), P<0.0001
CA9-24n/N (%)		
Varenicline	256/1005 (25.5%)	189/1032 (18.3%)
Bupropion	188/1001 (18.8%)	142/1033 (13.7%)
NRT	187/1013 (18.5%)	133/1025 (13.0%)

Placebo	106/1009 (10.5%)	85/1026 (8.3%)
Treatment Comparisons: Odds ratio (95% CI), p value		
Varenicline vs Placebo	2.99 (2.33, 3.83), P<0.0001	2.50 (1.90, 3.29), P<0.0001
Bupropion vs Placebo	2.00 (1.54, 2.59), P<0.0001	1.77 (1.33, 2.36), P<0.0001
NRT vs Placebo	1.96 (1.51, 2.54), P<0.0001	1.65 (1.24, 2.20), P=0.0007
Varenicline vs Bupropion	1.49 (1.20, 1.85), P=0.0003	1.41 (1.11, 1.79), P=0.0047
Varenicline vs NRT	1.52 (1.23, 1.89), P=0.0001	1.51 (1.19, 1.93), P=0.0008

CA = continuous abstinence rate; CI = confidence interval; NRT=Nicotine replacement therapy patch

Neuropsychiatric Safety Meta-analyses and Observational Studies:
Analyses of clinical trial data did not show evidence of an increased risk of serious neuropsychiatric events with varenicline compared to placebo. In addition, independent observational studies have not supported an increased risk of serious neuropsychiatric events in patients treated with varenicline compared to patients prescribed nicotine replacement therapy (NRT) or bupropion.

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

Analyses of Clinical Trials:

A meta-analysis of 5 randomised, double-blind, placebo controlled trials, including 1907 patients (1130 varenicline, 777 placebo), was conducted to assess suicidal ideation and behaviour as reported on the Columbia-Suicide Severity Rating Scale (C-SSRS). This meta-analysis included one trial (N=127) in patients with a history of schizophrenia or schizoaffective disorder and another trial (N=525) in patients with a history of depression. The results showed no increase in the incidence of suicidal ideation and/or behaviour in patients treated with varenicline compared to patients treated with placebo, as shown in the table below. Of the 55 patients who reported suicidal ideation or behaviour, 48 (24 varenicline, 24 placebo) were from the two trials that enrolled patients with a history of schizophrenia/ schizoaffective disorder, or of depression. Few patients reported these events in the other three trials (4 varenicline, 3 placebo).

Number of Patients and Risk Ratio for Suicidal Ideation and/or Behaviour Reported on C-SSRS from a Meta-Analysis of 5 Clinical Trials Comparing Varenicline to Placebo:

	Varenicline (N=1130)	**Placebo** (N=777)
Patients with suicidal ideation and/or behaviour* [n (%)]**	28 (2.5)	27 (3.5)
Patient-years of exposure	325	217
Risk Ratio # (RR; 95% CI)	0.79 (0.46, 1.36)	

* Of these, one patient in each treatment arm reported suicidal behaviour
** Patients with events up to 30 days after treatment; % are not weighted by study
# RR of incidence rates per 100 patient years

A meta-analysis of 18 double-blind, randomised, placebo-controlled clinical trials was conducted to assess the neuropsychiatric safety of varenicline. These trials included the 5 trials described above that used the C-SSRS, and a total of 8521 patients (5072 varenicline, 3449 placebo), some of which had psychiatric conditions. The results showed a similar incidence of combined neuropsychiatric adverse events, other than sleep disorders, in patients treated with varenicline compared to patients treated with placebo, with a risk ratio (RR) of 1.01 (95% CI: 0.89-1.15). Pooled data from these 18 trials showed a similar incidence rate of individual categories of psychiatric events in patients treated with varenicline compared to patients treated with placebo. The table below describes the most frequently (≥ 1%) reported categories of adverse events related to psychiatric safety other than sleep disorders and disturbances.

Psychiatric Adverse Events Occurring in ≥ 1% of Patients from Pooled Data from 18 Clinical Trials:

	Varenicline (N=5072)	**Placebo** (N=3449)
Anxiety disorders and symptoms	253 (5.0)	206 (6.0)
Depressed mood disorders and disturbances	179 (3.5)	108 (3.1)
Mood disorders and disturbances NEC*	116 (2.3)	53 (1.5)

* NEC = Not Elsewhere Classified

Counts (percentages) corresponds to the number of patients reporting the event

Observational Studies

Four observational studies, each including 10,000 to 30,000 users of varenicline in the adjusted analyses, compared the risk of serious neuropsychiatric events, including neuropsychiatric hospitalizations and fatal and non-fatal self-harm, in patients treated with varenicline versus patients prescribed NRT or bupropion. All studies were retrospective cohort studies and included patients with and without a psychiatric history. All studies used statistical methods to control for confounding factors, including preferential prescribing of varenicline to healthier patients, although there is the possibility of residual confounding.

Two of the studies found no difference in risk of neuropsychiatric hospitalisations between varenicline users and nicotine patch users (Hazard Ratio [HR] 1.14; 95% Confidence Interval [CI]: 0.56-2.34 in the first study, and 0.76; 95% CI: 0.40-1.46 in the second study). The power to detect differences in these two studies was limited. The third study reported no difference in risk of psychiatric adverse events diagnosed during an emergency department visit or inpatient admission between varenicline users and bupropion users (HR 0.85; 95% CI: 0.55-1.30). Based on post marketing reports, bupropion may be associated with neuropsychiatric adverse events.

The fourth study showed no evidence of a higher risk of fatal and non-fatal self- harm (HR of 0.88; 95% CI: 0.52-1.49) in patients prescribed varenicline compared to patients prescribed NRT. The occurrence of detected suicide was rare during the three months after patients initiated any drug treatment (two cases in 31,260 varenicline users and six cases in 81,545 NRT users).

Pregnancy Cohort Study

A population-based cohort study compared infants exposed to Varenicline in utero (N=335) with infants born to mothers who smoked during pregnancy (N=78,412) and infants born to non-smoking mothers (N=806,438). In this study, infants exposed to Varenicline in utero as compared to infants born to mothers who smoked during pregnancy had lower rates of congenital malformations (3.6% vs 4.3%), stillbirth (0.3% vs 0.5%), preterm birth (7.5% vs 7.9%), small for gestational age (12.5% vs 17.1%), and premature rupture of membrane (3.6% vs 5.4%).

Paediatric Population

The efficacy and safety of varenicline was evaluated in a randomised, double-blind, placebo-controlled study of 312 patients aged 12 to 19 years, who smoked an average of at least 5 cigarettes per day during the 30 days prior to recruitment, and had a score of at least 4 on the Fagerstrom Test for Nicotine Dependence scale. Patients were stratified by age (12-16 years of age and 17-19 years of age) and by body weight (≤55 kg and >55 kg). Following two-week titration, patients randomised to varenicline with a body weight >55 kg received 1 mg twice daily (high dose group) or 0.5 mg twice daily (low dose group), while patients with a body weight ≤55 kg received 0.5 mg twice daily (high dose group) or 0.5 mg once daily (low dose group). Patients received treatment for 12 weeks, followed by a non-treatment period of 40 weeks, along with age-appropriate counseling throughout the study.

The following table from the above paediatric study shows a comparison of continuous abstinence rates (CAR) from weeks 9-12, confirmed by urine cotinine test, for the full analysis set overall study population and the 12-17 year old population.

CAR9-12 (%)	**Overall n/N(%)**	**12-to-17-YearOlds n/N(%)**
High-Dose Varenicline	22/109 (20.2%)	15/80 (18.8%)
Low-Dose Varenicline	28/103 (27.2%)	25/78 (32.1%)
Placebo	18/100 (18.0%)	13/76 (17.1%)

Treatment Comparisons Odds ratio in CAR 9-12 (95% CI) [p-value]

High-Dose Varenicline vs Placebo	1.18 (0.59, 2.37) [0.6337]	1.13 (0.50, 2.56) [0.7753]
Low-Dose Varenicline vs Placebo	1.73 (0.88, 3.39) [0.1114]	2.28 (1.06, 4.89) [0.0347]*

**This p value is not considered statistically significant. The prespecified statistical testing procedures stopped testing after the high-dose varenicline vs Placebo treatment comparison in the overall study did not achieve statistical significance.*

CI=confidence interval; N=number of subjects randomised; n=the number of subjects who, at each visit from weeks 9 to 12 (inclusive), reported no smoking and no use of other nicotine-containing products since the last study visit/last contact (on the Nicotine Use Inventory) and at any of these visits were confirmed to have quit based on urine cotinine test.

5.2 Pharmacokinetic properties

Absorption

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

Distribution

Varenicline distributes into tissues, including the brain. Apparent volume of distribution averaged 415 litres (%CV= 50) at steady-state. Plasma protein binding of varenicline is low (< 20%) and independent of both age and renal function. In rodents, varenicline is transferred through the placenta and excreted in milk.

Biotransformation

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

In vitro studies demonstrate that varenicline does not inhibit cytochrome P450 enzymes (IC50 > 6,400 ng/ml). The P450 enzymes tested for inhibition were: 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4/5. Also, in human hepatocytes in vitro, varenicline was shown to not induce the activity of cytochrome P450 enzymes 1A2 and 3A4. Therefore, varenicline is unlikely to alter the pharmacokinetics of compounds that are primarily metabolised by cytochrome P450 enzymes.

Elimination

The elimination half-life of varenicline is approximately 24 hours. Renal elimination of varenicline is primarily through glomerular filtration along with active tubular secretion via the organic cationic transporter, OCT2 (see section 4.5).

Linearity/Non linearity

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

Pharmacokinetics in special patient populations

There are no clinically meaningful differences in varenicline pharmacokinetics due to age, race, gender, smoking status, or use of concomitant medicinal products, as demonstrated in specific pharmacokinetic studies and in population pharmacokinetic analyses.

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

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

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

Single and multiple-dose pharmacokinetics of varenicline have been investigated in paediatric patient aged 12 to 17 years old (inclusive) and were approximately dose-proportional over the 0.5 mg to 2 mg daily dose range studied. Steady-state systemic exposure in adolescent patients of bodyweight > 55 kg, as assessed by AUC (0-24), was comparable to that noted for the same doses in the adult population. When 0.5 mg twice daily was given, steady-state daily exposure of varenicline was, on average, higher (by approximately 40%) in adolescent patients with bodyweight ≤ 55 kg compared to that noted in the adult population. Varenicline is not recommended in paediatric patients because its efficacy in this population was not demonstrated (see sections 4.2 and 5.1).

5.3 Preclinical safety data

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Cellulose, microcrystalline
Croscarmellose sodium
Maltodextrin
Stearic acid

Tablet coating:
Opdry clear 04K59023:
Hypromellose
Triacetin

Opadry blue 03F505152:
Hypromellose
Macrogol
Titanium dioxide (E171)
Talc
FD&C blue #2 indigo carmine aluminum lake (E132)
FD&C blue #1/brilliant blue FCF aluminum lake (E133)
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Blister and bottle pack: 2 years
Bottle pack: In-use shelf life: 60 Days.

6.4 Special precautions for storage

Blisters and HDPE Bottle: Store below 25°C. Store in the original package in order to protect from light.

6.5 Nature and contents of container

Varenicline tablets are presented in PVC/Al blisters pack or high-density polyethylene (HDPE) bottles with polypropylene child resistant closure in the following pack sizes (not all presentations marketed):

Maintenance packs

- A carton containing PVC blisters with aluminium foil backing in a pack containing 28 and 56 x 1 mg film-coated tablets in card packaging.

- PVC blisters with aluminium foil backing in a pack containing 28, 56, 112 and 140 x 1 mg film-coated tablets in a carton.
- High-density polyethylene (HDPE) bottle with polypropylene child resistant closure containing 56 x 1 mg film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Ascend GmbH
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Frankfurt Am Main
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8 MARKETING AUTHORISATION NUMBER

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