NEW ZEALAND DATA SHEET
VARENICLINE SANDOZ® (VARENICLINE, AS CITRATE)

1. PRODUCT NAME

Varenicline Sandoz (varenicline, as citrate) 0.5 mg and 1 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 0.5 mg or 1 mg varenicline (as citrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

0.5 mg, white , capsule shaped film-coated tablet debossed with "0.5" on one side and plain on the other side.

1 mg, light blue, capsule shaped film-coated tablet debossed with "1.0" on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

Varenicline Sandoz is indicated as an aid to smoking cessation.

4.2. DOSE AND METHOD OF ADMINISTRATION

Adults

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

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

Days 1 – 3:	0.5 mg one daily
Days 4 – 7:	0.5 mg twice daily
Day 8 – End of Treatment:	1 mg twice daily

The patient should set a date to stop smoking. Varenicline Sandoz dosing should start 1 – 2 weeks before this date. Alternatively, a flexible approach to quitting smoking may be adopted. Patients can begin varenicline dosing and then quit smoking between days 8 and 35 of treatment (see section 5.1, Clinical Efficacy and Safety, Flexible Quit Date Study).

Patients who cannot tolerate adverse effects of varenicline may have the dose lowered temporarily or permanently.

Patients should be treated with Varenicline Sandoz 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 Sandoz at 1 mg twice daily is recommended to further increase the likelihood of long-term abstinence.

A gradual approach to quitting smoking with varenicline 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 for an additional 12 weeks for a total of 24 weeks of treatment (see section 5.1, Clinical Efficacy and Safety, Gradual Approach to Quitting Smoking Study).

Patients who are motivated to quit and who do not succeed in stopping smoking during prior varenicline 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 (see section 5.1, Clinical Efficacy and Safety, Study in Subjects Re-treated with Varenicline).

Dose tapering of Varenicline Sandoz is not required at the end of treatment.

Renal Impairment

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

For patients with severe renal impairment, the recommended dose of Varenicline Sandoz is 1 mg once daily. Dosing should begin at 0.5 mg once daily for the first 3 days then increased to 1 mg once daily (see section 5.2).

Based on insufficient clinical experience with Varenicline Sandoz in patients with end stage renal disease, treatment is not recommended in this patient population (see section 5.2, Special Patient Populations).

Hepatic Impairment

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

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.

Paediatric Population

Varenicline Sandoz is not recommended for use in paediatric patients because its efficacy in this population was not demonstrated (see section 5.1, Clinical Efficacy and Safety, Paediatric Population and see section 5.2, Paediatric Population).

Method of Administration

Varenicline Sandoz tablets should be swallowed whole with water.

Varenicline Sandoz 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

Effects of Smoking Cessation

Physiological changes resulting from smoking cessation, with or without treatment with Varenicline Sandoz, may alter pharmacokinetics or pharmacodynamics of some drugs, for which dosage adjustment may be necessary (examples include theophylline, warfarin and insulin). 1As smoking induces CYP1A2, smoking cessation may result in an increase of plasma levels of CYP1A2 substrates.

Smoking cessation, with or without pharmacotherapy, has been associated with change in appetite and weight gain.

Smoking cessation, with or without pharmacotherapy, has been associated with the exacerbation of underlying psychiatric illness (e.g. depression). Care should be taken with patients with a history of psychiatric illness and patients should be advised accordingly.

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.

Psychiatric Symptoms

Serious neuropsychiatric symptoms, including changes in behaviour or thinking, anxiety, psychosis, mood swings, agitation, aggression, depressed mood, suicidal ideation and suicidal behaviour have been reported in patients attempting to quit smoking with varenicline. Patients and their families should be advised that the patient should stop taking Varenicline Sandoz and contact a healthcare professional immediately if such symptoms are observed.

Doctors should discuss the efficacy and safety profile of Varenicline Sandoz with patients attempting to quit smoking with Varenicline Sandoz and advise them of the possible emergence of neuropsychiatric symptoms. Patients and their families should be alerted to the need to monitor for the possible emergence of neuropsychiatric symptoms. Patients and their families should be encouraged to report any history of psychiatric illness prior to initiating treatment.

A causal association between varenicline and these symptoms has not been established, although association cannot be excluded. Doctors and other healthcare professionals should continue to monitor patients for the development of neuropsychiatric symptoms. On-going follow up of patients with these symptoms should be provided until the symptoms resolve.

A large randomized, 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, Clinical Efficacy and Safety, Neuropsychiatric Safety and section 4.8, Special Populations).

Analyses of pooled 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 (see section 5.1, Clinical Efficacy and Safety, Neuropsychiatric Safety).

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. A causal relationship between these reports and varenicline use has not been established.

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 Sandoz and contact a health care provider immediately (see section 4.8, Post-Marketing Experience).

There have also been post-marketing reports of rare but severe cutaneous reactions, including Stevens-Johnson Syndrome and Erythema Multiforme in patients using 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(see section 4.8, Post-Marketing Experience).

Cardiovascular Events

In a smoking cessation study in patients with stable cardiovascular (CV) disease and in a meta-analysis of 15 clinical trials, some CV events were reported more frequently in patients treated with varenicline compared to placebo. These events occurred primarily in patients with known CV disease. No causal relationship between these events and varenicline has been established. In a large smoking cessation trial that assessed CV safety in patients with and without a history of psychiatric disorder, major CV events (CV death, non-fatal MI, non-fatal stroke) were reported less frequently in patients treated with varenicline compared to placebo. In these studies, major CV events were infrequent overall and all-cause and CV mortality was lower in patients treated with varenicline compared to patients treated with placebo. Smoking is an independent and major risk factor for CV disease. Patients should be instructed to notify their health care providers 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, Cardiac Safety Assessment Study). Smoking is an independent and major risk factor for cardiovascular disease.

4.5. INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Each Varenicline Sandoz tablet contains varenicline (as citrate). The innovator product contains varenicline (as tartrate). All clinical data in this product information are based on varenicline (as tartrate). Bioequivalence with respect to varenicline has been established between the two salt forms.

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

In vitro studies demonstrate that varenicline tartrate does not inhibit cytochrome P450 enzymes (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 not to induce the activity of cytochrome P450 enzymes 1A2 and 3A4. Therefore, varenicline tartrate is unlikely to alter the pharmacokinetics of compounds that are primarily metabolised by cytochrome P450 enzymes.

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

In vitro studies demonstrate that active renal secretion of varenicline tartrate is mediated by the human organic cation transporter, OCT2. Co-administration with inhibitors of OCT2 does not require a dose adjustment of varenicline as the increase in systemic exposure to varenicline tartrate is not expected to be clinically meaningful (see cimetidine interaction below). Furthermore since metabolism of varenicline tartrate contributes to less than 10% of its clearance, drugs known to affect the cytochrome P450 system are unlikely to alter the pharmacokinetics of varenicline tartrate (see section 5.2) and therefore a dose adjustment of Varenicline Sandoz would not be required.

Metformin

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

Cimetidine

Co-administration of an OCT2 inhibitor, cimetidine (300 mg four times daily), with varenicline (2 mg single dose) increased the systemic exposure of varenicline by 29% due to a reduction in varenicline renal clearance. No dosage adjustment is recommended based on concomitant cimetidine administration in subjects with normal renal function or in patients with mild to moderate renal impairment. In patients with severe renal impairment, the concomitant use of cimetidine and varenicline should be avoided.

Digoxin

Varenicline tartrate (1 mg twice daily) did not alter the steady-state pharmacokinetics of digoxin administered as a 0.25 mg daily dose.

Warfarin

Varenicline tartrate (1 mg twice daily) did not alter the pharmacokinetics of a single 25 mg dose of (R,S)-warfarin. Prothrombin time (INR) was not affected by varenicline tartrate. Smoking cessation itself may result in changes to warfarin pharmacokinetics (see 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 or neuropsychiatric events in patients drinking alcohol during varenicline treatment. A causal relationship between these events and varenicline use has not been established.

Use with Other Therapies for Smoking Cessation

<u>Bupropion</u>

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

<u>Nicotine replacement therapy (NRT)</u>

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

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

4.6. FERTILITY, PREGNANCY AND LACTATION

Use in pregnancy

Pregnancy Category: B3

A moderate amount of data on pregnant women (between 300-1000 pregnancy outcomes) indicated no malformative or fetal/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).

Women of Child Bearing Potential

Where drug therapy is initiated, treatment should be timed such that the course is completed before conception.

Effects on fertility

It is not expected that varenicline tartrate would impair fertility. Varenicline did not impair fertility in rats at oral doses producing plasma concentrations up to 40 times the human plasma Cmax at the maximal recommended dose of 1 mg twice daily (see section 4.6, Pregnancy).

Use in lactation

It is not known whether varenicline is excreted in human milk. Because many drugs are excreted in human milk and because the potential for adverse effects in nursing infants from Varenicline Sandoz is unknown, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

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. No attempt has been made in either the design or the analysis of the varenicline studies to distinguish between adverse effects associated with study drug treatment or those possibly associated with nicotine withdrawal.

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

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

Table 1 includes the most frequently occurring events (at a rate of ≥1% and an incidence higher than that for placebo) based on evaluation of data from pre-marketing phase 2- 3 studies and updated based on pooled data from 19 placebo-controlled pre- and post- marketing studies, including approximately 5,800 patients treated with varenicline.

Table 1 Treatment-emergent all-causality Adverse Events reported in studies at a rate ≥1%

	Percentage of Patients Reporting Event	
	Varenicline N=5823	**Placebo N=4191**
Gastrointestinal Disorders		
Nausea	28.2	9.6
Abdominal pain [a]	6.6	3.9
Constipation	6.3	2.9
Diarrhoea	4.4	3.8
Vomiting	4.5	1.8
Dyspepsia	4.3	2.4
Flatulence	4.1	2.1
Dry mouth	3.8	2.9
Abdominal Distension	1.8	0.9
Toothache	1.2	1.0
Gastro-oesophageal reflux disease	1.0	0.6
General Disorders and Administration Site Conditions		
Fatigue	5.0	4.1
Chest pain	1.1	0.9
Infections and Infestations		
Nasopharyngitis	11.0	8.9
Influenza	3.1	2.9
Sinusitis	1.6	1.7
Bronchitis	1.3	1.8
Gastroenteritis	1.1	1.0
Metabolism and Nutrition Disorders		
Increased Appetite	3.5	2.3
Weight increased	2.2	1.1
Decreased appetite	1.8	1.6
Nervous System Disorders		
Headache	13.9	11.0
Dizziness	4.8	5.3
Dysgeusia	3.9	2.4
Somnolence	3.0	2.0
Disturbance in Attention	2.4	2.5
Psychiatric Disorders		
Insomnia [b]	14.1	8.7
Abnormal Dreams [c]	11.0	4.6
Irritability	5.0	4.6
Anxiety	3.5	4.9
Sleep Disorder	3.6	2.4
Depression	2.1	2.3
Depressed mood	1.6	1.5
Agitation	1.2	1.1

Table 1 Treatment-emergent all-causality Adverse Events reported in studies at a rate ≥1%

	Percentage of Patients Reporting Event	
	Varenicline N=5823	**Placebo N=4191**
Respiratory, Thoracic and Mediastinal Disorders		
Cough	2.3	2.6
Oropharyngeal pain	1.8	1.5
Dyspnoea	1.2	0.6
Skin and Subcutaneous Tissue Disorders		
Rash	1.4	1.2
Pruritis [d]	1.0	0.6
Musculoskeletal and Connective Tissue Disorders		
Back pain	3.4	3.0
Arthralgia	1.9	1.5
Myalgia	1.4	0.9
Pain in extremity	1.2	1.2
Vascular Disorders		
Hypertension	1.2	1.1

a. Includes PTs Abdominal pain, Gastrointestinal pain Abdominal tenderness, Abdominal pain lower, Abdominal pain upper and Abdominal discomfort

b. Includes PTs Insomnia, Initial insomnia, Middle insomnia and Terminal insomnia

c. Includes PTs Abnormal dreams and Nightmare

d. Includes PTs Pruritus and Pruritus generalized

In Table 2 below, all adverse reactions, which occurred at a rate < 1% are listed by system organ class and frequency (uncommon ≥1/1,000 to <1/100, rare: ≥1/10,000 to <1/1000).

Table 2 Adverse Reactions Reported in Studies at a Rate <1%

System Organ Class	*Adverse Drug Reactions*
Blood and Lymphatic System Disorders	
Rare	Platelet count decreased
Metabolism and Nutrition Disorders	
Rare	Polydipsia
Psychiatric Disorders	
Uncommon	Thinking abnormal, mood swings, restlessness, libido decreased
Rare	Bradyphrenia, dysphoria
Nervous System Disorders	
Uncommon	Tremor, hypoaesthesia, lethargy, hypogeusia
Rare	Circadian rhythm sleep disorder, dysarthria, coordination abnormal, visual field defect
Cardiac Disorders	
Uncommon	Angina pectoris, tachycardia, palpitations, heart rate increased
Rare	Electrocardiogram T wave amplitude decreased, atrial fibrillation, electrocardiogram ST segment depression
Vascular Disorders	
Uncommon	Hot flush, blood pressure increased
Eye Disorders	
Uncommon	Conjunctivitis, eye pain
Rare	Photophobia,
Ear and Labyrinth Disorders	
Uncommon	Tinnitus
Respiratory, Thoracic and Mediastinal Disorders	
Uncommon	Throat irritation, respiratory tract congestion, sinus congestion, upper- airway cough syndrome, rhinorrhoea, rhinitis allergic, upper respiratory tract inflammation, dysphonia
Rare	Snoring
Gastrointestinal Disorders	
Uncommon	Haematochezia, gastritis, eructation, aphthous stomatitis, gingival pain
Rare	Haematemesis
Skin and Subcutaneous Tissue Disorders	
Uncommon	Erythema, acne, hyperhidrosis
Musculoskeletal and Connective Tissue Disorders	
Uncommon	Muscle spasms
Rare	Joint stiffness
Renal and Urinary Disorders	
Uncommon	Pollakiuria, nocturia, polyuria
Rare	Glycosuria
Reproductive System and Breast Disorders	
Uncommon	Menorrhagia
Rare	Sexual dysfunction
General Disorders and Administration Site Conditions	
Uncommon	Chest discomfort, pyrexia, asthenia, malaise, influenza like illness
Investigations	
Uncommon	Liver function test abnormal

Special Populations

Studies have been conducted on patients with and without a history of psychiatric disorder, with cardiovascular disease (CV), chronic obstructive pulmonary disease (COPD), major depressive disorder (MDD) and stable schizophrenia or schizoaffective disorder (see section 5.1**,** Clinical Efficacy and Safety).

Patients with and without a History of Psychiatric Disorder

Adverse events from the neuropsychiatric (NPS) safety study are presented in the following tables.

Table 3 shows the rates of the composite NPS adverse event primary end point by treatment group and the risk differences (RDs) (95% CI) vs placebo in the non-psychiatric cohort. The individual components of the endpoint are also shown. In addition, the table shows the subset of the endpoint comprised of only events of severe intensity:

Table 3 Composite NPS Adverse Event Primary End Point By Treatment Group - Non-psychiatric Cohort

	Non-psychiatric Cohort N=3984			
	Varenicline	**Bupropion**	**NRT**	**Placebo**
Number of Patients Treated	990	989	1006	999
Composite NPS AE Primary Endpoint, 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)	
NPS AE Primary Endpoint Components, n (%):				
Anxiety [a]	0	1 (0.1)	0	3 (0.3)
Depression [a]	1 (0.1)	0	0	0
Feeling abnormal [a]	0	0	0	0
Hostility [a]	0	1 (0.1)	1 (0.1)	0
Agitation [b]	10 (1.0)	11 (1.1)	19 (1.9)	11 (1.1)
Aggression [b]	3 (0.3)	3 (0.3)	2 (0.2)	3 (0.3)
Delusions [b]	0	0	1 (0.1)	0
Hallucinations [b]	1 (0.1)	0	0	0
Homicidal ideation [b]	0	0	1 (0.1)	0
Mania [b]	0	1 (0.1)	2 (0.2)	2 (0.2)
Panic [b]	0	4 (0.4)	1 (0.1)	3 (0.3)
Paranoia [b]	0	1 (0.1)	0	0
Psychosis [b]	0	0	1 (0.1)	0
Suicidal behaviour [b]	0	1 (0.1)	1 (0.1)	0
Suicidal ideation [b]	0	1 (0.1)	2 (0.2)	3 (0.3)
Completed suicide [b]	0	0	0	1 (0.1)
Composite NPS AE Endpoint of severe intensity n (%)	1 (0.1)	4 (0.4)	3 (0.3)	5 (0.5)

NPS AE Endpoint Components of severe intensity, n (%):				
Anxiety [a]	0	1 (0.1)	0	3 (0.3)
Depression [a]	1 (0.1)	0	0	0
Feeling abnormal [a]	0	0	0	0
Hostility [a]	0	1 (0.1)	1 (0.1)	0
Agitation [a]	0	0	2 (0.2)	0
Aggression [a]	1 (0.1)	1 (0.1)	0	0
Delusions [a]	0	0	0	0
Hallucinations [a]	0	0	0	0
Homicidal ideation [a]	0	0	0	0
Mania [a]	0	0	0	0
Panic [a]	0	1 (0.1)	1 (0.1)	1 (0.1)
Paranoia [a]	0	0	0	0
Psychosis [a]	0	0	0	0
Suicidal behaviour [a]	0	1 (0.1)	0	0
Suicidal ideation [a]	0	0	0	1 (0.1)
Completed suicide [a]	0	0	0	1 (0.1)

AE=adverse event; [a] Grade=severe intensity AE; [b] Grade=moderate and severe intensity AE; NRT=Nicotine replacement therapy patch

In the non-psychiatric cohort, 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: risk differences (RDs (95% Confidence Interval [CI])) vs placebo were -1.28% (-2.40, -0.15) for varenicline, -0.08% (-1.37, 1.21) for bupropion and -0.21% (-1.54, 1.12) for NRT. The use of varenicline, bupropion and NRT in the non-psychiatric cohort was not associated with an increased risk of NPS adverse events in the composite primary endpoint compared with placebo (95% CIs were lower than or included zero). Similarly, the use of varenicline was not associated with an increased risk of NPS adverse events in the composite primary endpoint compared with bupropion or NRT in the non-psychiatric cohort (-1.19% (-2.30, -0.09) and -1.07 (-2.21, 0.08), respectively).

In the non-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:

Table 4 Patients with Suicidal Ideation and/or Behaviour - Non-psychiatric Cohort

	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)

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 end point by treatment group and the risk differences (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 endpoint comprised of only events of severe intensity:

Table 5 Composite NPS Adverse Event Primary End Point By Treatment Group - Psychiatric Cohort

	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)

NPS AE Endpoint Components of severe intensity 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 [a]	1 (0.1)	1 (0.1)	4 (0.4)	2 (0.2)
Aggression [a]	1 (0.1)	1 (0.1)	0	1 (0.1)
Delusions [a]	0	0	0	0
Hallucinations [a]	0	1 (0.1)	0	0
Homicidal ideation [a]	0	0	0	0
Mania [a]	2 (0.2)	0	0	0
Panic [a]	0	1 (0.1)	0	1 (0.1)
Paranoia [a]	0	1 (0.1)	0	0
Psychosis [a]	0	0	0	0
Suicidal ideation [a]	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)
Completed suicide [a]	1 (0.1)	0	1 (0.1)	0
	0	0	0	0

AE=adverse event; [a] Grade=severe intensity AE; [b] Grade=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. In the psychiatric cohort, the incidence of events in the composite endpoint was higher for each of the active treatments compared to placebo: RDs (95% CI) vs placebo were 1.59% (-0.42, 3.59) for varenicline, 1.78% (-0.24, 3.81) for bupropion and 0.37% (-1.53, 2.26) for NRT. The use of varenicline, bupropion and NRT in the psychiatric cohort was not associated with an increased risk of NPS adverse events in the composite primary endpoint compared with placebo (95% CIs included zero). Similarly, the use of varenicline was not associated with an increased risk of NPS adverse events in the composite primary endpoint compared with bupropion or NRT in the psychiatric cohort (-0.20% (-2.34, 1.95) and 1.22% (-0.81, 3.25), respectively).

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:

Table 6 Patients with Suicidal Ideation and/or Behaviour - Psychiatric Cohort

	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. Adverse events reported in ≥ 10% of subjects treated with varenicline in the entire study population were nausea (25.3% vs 6.8% on placebo) and headache (12.2% vs 9.9% on placebo).

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 neuropsychiatric symptoms, some serious, as well as worsening of pre-existing psychiatric illness such as depressed mood, agitation, hallucinations, changes in behaviour or thinking, anxiety, psychosis, mood swings, aggressive behaviour suicidal ideation and suicide in patients attempting to quit smoking while taking varenicline. Smoking cessation with or without treatment is associated with nicotine withdrawal symptoms and the exacerbation of underlying psychiatric illness. Not all patients had known pre-existing psychiatric illness and not all had discontinued smoking. The role of varenicline in these reports is not known (see section 4.4).

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).

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

There have also been post- marketing reports of nightmares, diabetes mellitus, hyperglycaemia and convulsions.

Reporting suspected adverse effects

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

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

Mechanism of action

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

Pharmacodynamic Effects

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

Clinical Efficacy and Safety

The efficacy of varenicline in smoking cessation was demonstrated in three pre- marketing clinical trials in which a total of 2619 chronic cigarette smokers (≥10 cigarettes per day) received varenicline. Two of these studies were double-blind comparisons between varenicline, bupropion and placebo, assessing critical aspects of smoking cessation, including end-of-treatment and long-term abstinence rates after 12 weeks of treatment. In addition, the effects on reducing craving and withdrawal that can occur during smoking cessation and the reinforcing effects that can perpetuate smoking behaviour were studied. The third study assessed the effect of an additional 12 weeks of treatment on maintaining long-term abstinence.

Clinical trials

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

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

smoking during the non- treatment phase.

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

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

Table 7 Continuous Quit Rates, Continuous Abstinence and Long Term Quit Rates for Studies 1 and 2

	Study 1 n=1022			Study 2 n=1023		
	4W CQR	**CA wk 9-52**	**LTQR wk 52**	**4W CQR**	**CA wk 9-52**	**LTQR wk 52**
Varenicline	44.4% [a]	22.1% [b]	25.5% [c]	44.0% [a]	23.0% [d]	25.4% [e]
Bupropion	29.5%	16.4%	17.9%	30.0%	15.0%	18.2%
Placebo	17.7%	8.4%	9.6%	17.7%	10.3%	12.6%

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

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

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

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

<u>Patient Reported Craving, Withdrawal and Reinforcing Effects of Smoking</u>

Across both Studies 1 and 2, craving and withdrawal were significantly reduced in patients randomized 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.

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

Table 8 Continuous Abstinence and Long Term Quit Rates for Maintenance of Abstinence Study

	Varenicline n=602	Placebo n=604
CA wk 13-24	70.6%*	49.8%
CA wk 13-52	44.0%**	37.1%
LTQR at week 52	47.8%***	40.7%

*p<0.0001 vs. placebo, **p=0.0126 vs. placebo, ***p=0.0119 vs. placebo

This study showed the benefit of an additional 12-week treatment with varenicline 1 mg twice daily for the maintenance of smoking cessation compared to placebo. The odds of maintained abstinence at week 24, following an additional 12 weeks of treatment with varenicline, were 2.47 times those for placebo (95% CI: 1.95, 3.15). Superiority to placebo for continuous abstinence was maintained through week 52 (Odds Ratio = 1.35, 95% CI: 1.07, 1.70).

Flexible Quit Date Study

The effect of varenicline 1 mg twice a day in a flexible, patient-selected quit date setting was assessed in a double-blind, placebo-controlled study of 651 subjects. Subjects were randomised 3:1 to varenicline or placebo for a treatment of 12 weeks and a followed up post-treatment for another 12 weeks. In this study, 486 subjects received varenicline and 165 received placebo. Subjects were instructed to select a quit date after the initial week of dose titration and before the clinical visit at the end of week 5 of treatment. Subjects treated with varenicline had a superior rate of CO-confirmed abstinence during weeks 9 through 12 (53.94%) compared to patients treated with placebo (19.4%) (odds ratio 6.03; 95% CI 3.80, 9.56; p<0.0001) and from week 9 through 24 (35.2%) compared to subjects treated with placebo (12.73%) (odds ratio 4.45; 95% CI 2.62, 7.55; p<0.0001). Adverse events in this study were quantitatively and qualitatively similar to those observed in premarketing studies. The key results are summarized in the following table:

Table 9 Rates of CO-confirmed abstinence for Flexibility in Setting a Quit Date Study

	Varenicline n=486	Placebo n=165	Odds ratio (95% CI), p value
CA wk 9-12	53.9%	19.4%	6.03 (3.80, 9.56) p<0.0001
CA wk 9-24	35.2%	12.7%	4.45 (2.62, 7.55) p<0.0001

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 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 (45.0%) compared to patients treated with placebo (11.8%) (odds ratio 7.08;
95% CI 4.34, 11.55; p<0.0001) and from weeks 9 through 52 (20.1%) compared to subjects treated with placebo (3.3%) (odds ratio 9.00; 95% CI 3.97, 20.41; 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:

Table 10 Rates of CO-confirmed Abstinence for Retreatment with Varenicline Study

	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

Gradual Approach to Quitting Smoking Study

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 randomized 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 at weeks 15 through 24 (32.1% vs 6.9%; odds ratio 8.74; 95% CI 6.09, 12.53; p<0.0001) and weeks 21 through 52 (27.0% vs 9.9%; odds ratio 4.02; 95% CI 2.94, 5.50; p<0.0001).

The varenicline safety profile in this study was consistent with the premarketing studies.

The key results are summarized in the following table:

Table 11 Rates of CO-confirmed abstinence for Gradual Approach to Quitting Study

	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

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 twice a day 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 hospitalization 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 revascularization (2.0% vs. 0.6%), hospitalization 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 revascularization underwent the procedure as part of management of nonfatal MI and hospitalization 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 (see section 4.4).

The key results are summarized in the following table:

Table 12 Rates of CO-confirmed abstinence for Study in Subjects with Cardiovascular Disease

	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

Cardiovascular Safety Assessment Study in Subjects with and without a History of Psychiatric Disorder

The cardiovascular (CV) safety of varenicline was evaluated in the Cardiovascular Safety Assessment Study in subjects with and without a history of psychiatric disorder (parent study) and in a non-treatment extension study. In the parent study (N=8058), 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 non-treatment extension study enrolled 4595 of the 6293 subjects who completed the parent study and followed them through week 52. Of all treated subjects, 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 event (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)	

Incidence of MACE + (defined as any MACE or a new onset or worsening peripheral vascular disease (PVD) requiring intervention, a need for coronary revascularization, or hospitalization for unstable angina) and all cause deaths are shown for all treatment groups during treatment, and cumulative for treatment plus 30 days and through end of study in the following table.

	Varenicline N=2016	**Bupropion N=2006**	**NRT N=2022**	**Placebo N=2014**
During treatment				
MACE+, n (%)	5 (0.25)	4 (0.20)	2 (0.10)	5 (0.25)
All cause deaths, n (%)	0	2 (0.10)	0	2 (0.10)
During treatment plus 30 days				
MACE+, n (%)	5 (0.25)	4 (0.20)	3 (0.15)	7 (0.35)
All cause deaths, n (%)	0	2 (0.10)	0	2 (0.10)
Through end of study				
MACE+, n (%)	10 (0.50)	15 (0.75)	10 (0.49)	12 (0.60)
All cause deaths, n (%)	2 (0.10)	4 (0.20)	3 (0.15)	4 (0.20)

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. The number of subjects with MACE, MACE + and all cause deaths was similar or lower for the varenicline-treated subjects compared to those treated with placebo (see section 4.4).

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 twice a day 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 summarized in the following table:

Table 13 Rates of CO-confirmed abstinence for Study in Subjects with Obstructive Pulmonary Disease

	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 Major Depressive Disorder

Varenicline was evaluated in a randomised, double-blind, placebo-controlled study of 525 subjects with major depressive disorder without psychotic features (DSM-IV TR), on stable antidepressant treatment and/or who experienced a major depressive episode in the past 2 years and were successfully treated. Subjects aged 18 to 75 years were randomised to varenicline 1 mg BID or placebo for a treatment of 12 weeks and then followed for 40 weeks post-treatment. Subjects treated with varenicline had a superior rate of CO-confirmed abstinence during weeks 9 through 12 (35.9%) compared to subjects treated with placebo (15.6%) (odds ratio 3.35; 95% CI 2.16, 5.21; p<0.0001) and from week 9 through 52 (20.3%) compared to subjects treated with placebo (10.4%) (odds ratio 2.36; 95% CI 1.40, 3.98; p=0.0011).

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%). Additionally, the following psychiatric AEs were reported in ≥ 2% of patients in either treatment group (varenicline or placebo, respectively): anxiety (7.0% vs. 9.3%), agitation (6.6% vs. 4.1%), depression (6.6% vs. 4.8%), tension (3.5% vs. 3.0%), depressed mood (2.7% vs. 3.7%), sleep disorder (2.7% vs. 1.5%), hostility (2.0% vs. 0.4%) and restlessness (2.0% vs. 1.9%). Psychiatric scales showed no differences between the varenicline and placebo groups and no overall worsening of depression during the study in either treatment group.

The percentage of subjects with suicidal ideation and/or behaviour was similar between the varenicline and placebo groups during treatment (6.0% and 7.5%, respectively) and the non-treatment follow-up (6.2% and 5.8%, respectively). There was one event of intentional self injury/possible suicide attempt during treatment (Day 73) in a subject with history of alcohol abuse in the placebo group. A possible suicide could not be ruled out in one subject who died by an overdose of illicit drugs 76 days after last dose of study drug in the varenicline group.

The key efficacy results are summarised in the following table:

Table 14 Rates of CO-confirmed abstinence for Patients with Major Depressive Disorder

	Varenicline n=256	Placebo n=269	Odds ratio (95% CI), p value
CA wk 9-12	35.9	15.6	3.35 (2.16, 5.21) p<0.0001
CA wk 9-52	20.3	10.4	2.36 (1.40, 3.98) p=0.0011

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, randomized 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 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 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.

Neuropsychiatric Safety

Study in Patients with and without a History of Psychiatric Disorder

Varenicline was evaluated in a randomized, 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 randomized 1:1:1:1 to varenicline 1 mg twice a day, bupropion SR 150 mg twice a day, 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 moderate or severe events of agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal ideation, suicidal behaviour or completed suicide (see section 4.4).

The most commonly reported adverse events in subjects treated with varenicline in this study were similar to those observed in premarketing studies. Adverse events reported in ≥ 10% of subjects treated with varenicline in the entire study population were nausea (25.3% vs 6.8% on placebo) and headache (12.2% vs 9.9% on placebo) (see section 4.8, Special Populations).

In both cohorts, subjects treated with varenicline had a superior rate of CO-confirmed abstinence during weeks 9 through 12 and 9 through 24 compared to subjects treated with bupropion, nicotine patch and placebo.

The key efficacy results are summarized in the following table:

Table 15 Rates of CO-confirmed abstinence for Patients with and without a History of Psychiatric Disorder

	Non-psychiatric Cohort	**Psychiatric Cohort**
CAR 9-12 n/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
CAR 9-24 n/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

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

Meta-Analyses of Clinical Trials

A meta-analysis of 5 randomized, 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, with a Risk Ratio (RR) of 0.79 (95% Confidence Interval [CI]: 0.46, 1.36), as shown in the table below. Forty-eight (48) of the 55 patients who reported suicidal ideation or behaviour (24 varenicline, 24 placebo) were from the two trials that enrolled patients with a history of schizophrenia, schizoaffective disorder, or depression. Few patients reported these events in the other three trials (4 varenicline, 3 placebo).

Table 16 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, randomized, placebo-controlled clinical trials assessed 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: 0.88, 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.

Table 17 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 hospitalizations 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). 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).

Other Observational Studies

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* were no more likely to have major congenital malformations (3.6%) than infants born to mothers who smoked during pregnancy (4.3%) or to non-smoking mothers (4.2%). Similarly, infants exposed to varenicline *in utero*, as compared to infants of smoking and non-smoking mothers, were not at increased risk of stillbirth, (0.3%, 0.5%, 0.3%, respectively), small for gestational age (12.5%, 17.1%, 9.1%), preterm birth (7.5%, 7.9%, 5.8%), or premature rupture of membrane (3.6%, 5.4%, 3.8%) (see section 4.6).

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. Patients were stratified by age (12 to 16 years of age and 17 to 19 years of age) and by body weight (≤55 kg and >55 kg). Following a 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 counselling throughout the study.

Results from this study showed that neither varenicline dose significantly increased continuous abstinence rates at weeks 9 through 12 of treatment compared with placebo in subjects 12 to 19 years of age or in subjects 12 to 16 years of age. The study was not powered to assess efficacy in adolescent smokers 17 to 19 years of age, and in this group conclusions cannot be drawn. The varenicline safety profile in this study was consistent with that shown in adult studies (see section 4.2, Paediatric Population and section 5.2, Paediatric Population).

5.2. PHARMACOKINETIC PROPERTIES

Absorption

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

Distribution

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

Metabolism

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

Elimination

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

Special Patient Populations

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

Hepatic Impairment

Due to the absence of significant hepatic metabolism, varenicline pharmacokinetics should be unaffected in patients with hepatic insufficiency and the potential for clinically meaningful drug interactions between varenicline and metabolic inhibitors/inducers is low.

Renal Impairment

Varenicline tartrate pharmacokinetics were unchanged in subjects with mild renal impairment (estimated creatinine clearance >50 mL/min and ≤80 mL/min); in patients with moderate renal impairment (estimated creatinine clearance ≥30 mL/min and ≤50 mL/min), varenicline tartrate 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 tartrate exposure increased 2.1-fold. In subjects with end-stage-renal disease (ESRD), varenicline tartrate was efficiently removed by haemodialysis. While no dosing adjustment is necessary for patients with mild to moderate renal impairment, a reduced dosing frequency of 1 mg once daily is recommended for patients with severe renal impairment (see section 4.2). Dosing should begin at 0.5 mg once daily for the first 3 days, and then increased to 1 mg once daily.

Elderly (> 65 years)

No dosage adjustment is necessary for elderly patients (see section 4.2).

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

Paediatric Population

Varenicline Sandoz is not recommended for use in paediatric patients (under 18 years of age) because its efficacy in this population was not demonstrated.

Single and multiple-dose pharmacokinetics of varenicline have been investigated in paediatric subjects 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 a 0.5 mg dose was given twice a day, steady-state daily exposure of varenicline was, on average, higher (by approximately 40%) in adolescent patients with bodyweight ≤ 55 kg compared to that seen in the adult population (see section 4.2, Paediatric Population and section 5.1, Clinical Efficacy and Safety, Paediatric Population).

5.3. PRECLINICAL SAFETY DATA

Carcinogenicity

Carcinogenicity studies were performed in mice and rats at respective oral doses of varenicline up to 20 mg/kg/day and 15 mg/kg/day for 2 years, with respective systemic drug exposure (C_{max}) up to 130 and 50 times the human plasma C_{max} at the maximal recommended dose of 1 mg twice daily. There was no evidence of carcinogenicity in mice or female rats. Male rats showed increased incidences of hibernoma (a rare tumour of brown fat) at systemic exposures of 25 times the human C_{max} (incidence 1/65 rats) and 50 times the human C_{max} (incidence 2/65 rats); the no-effect exposure was 10 times the human C_{max}. The clinical relevance of this finding has not been established.

Genotoxicity

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

Teratogenesis

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

Nonteratogenic Effects

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

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

Microcrystalline cellulose

Pregelatinised starch

Propyl gallate

Citric acid

Magnesium stearate

Opadry® White (0.5 mg)

Opadry® Blue (1 mg)

6.2. INCOMPATIBILITIES

Not applicable

6.3. SHELF LIFE

24 months

6.4. SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5. NATURE AND CONTENTS OF CONTAINER

Varenicline Sandoz tablets are presented in blister strips in the following pack sizes:

- Initiation Pack containing 11 x 0.5 mg film-coated tablets and 42 x 1 mg film-coated tablets.
- Continuation Pack containing 56 x 1 mg film-coated tablets.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL

No special requirements.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Sandoz New Zealand Limited

12 Madden Street

Auckland 1010

New Zealand

Telephone: 0800 726 369

9. DATE OF FIRST APPROVAL

08/08/2024

10. DATE OF REVISION OF THE TEXT

08/08/2024

Section changed	Summary of new information