AUSTRALIAN PRODUCT INFORMATION - VARENICLINE VIATRIS (varenicline) TABLETS

1. NAME OF THE MEDICINE

Varenicline (as tartrate).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each VARENICLINE VIATRIS film-coated tablet contains either 0.5 mg or 1 mg

varenicline (as tartrate).

For the full list of excipients, see Section 6.1 - List of excipients.

3. PHARMACEUTICAL FORM

Film-coated tablets.

VARENICLINE VIATRIS is supplied for oral administration in two strengths:

- 0.5 mg white to off-white, capsule shape and biconvex film-coated tablets debossed with " *0.5*" on one side and plain on the other side.
- 1 mg light blue, capsule shape and biconvex film-coated tablets, debossed with " *1.0*" on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

4.2 Dose and Method of Administration

Use in Adults

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

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

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

The patient should set a date to stop smoking. VARENICLINE VIATRIS 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 – Pharmacodynamic Properties, Clinical Trials, Flexible Quit Date Study).

Patients should be treated with VARENICLINE VIATRIS 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 VIATRIS 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 by 50% from baseline within the first four weeks, by an additional 50% in the next four weeks, and continue reducing with the goal of reaching complete abstinence by 12 weeks. Patients should then continue taking varenicline for an additional 12 weeks for a total of 24 weeks of treatment (see Section 5.1 – Pharmacodynamic Properties, Clinical Trials, 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 – Pharmacodynamic Properties, Clinical Trials**,** Re-treatment with Varenicline Study).

VARENICLINE VIATRIS tablets should be swallowed whole with water. VARENICLINE VIATRIS can be taken with or without food.

Dose tapering of VARENICLINE VIATRIS is not required at the end of treatment.

Use in 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 VIATRIS is 1 mg once daily. Dosing should begin at 0.5 mg once daily for the first 3 days then increase to 1 mg once daily (see Section 5.2 - Pharmacokinetic Properties).

Based on insufficient clinical experience with varenicline in patients with end stage renal disease, treatment is not recommended in this patient population (see Section 5.2 - Pharmacokinetic Properties, Special Populations).

Use in Hepatic Impairment

No dosage adjustment is necessary for patients with hepatic impairment (see Section 5.2 - Pharmacokinetic Properties).

Use in the Elderly

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

Use in Paediatric and Adolescent Patients

Varenicline is not recommended for use in paediatric and adolescent patients because its efficacy in this population was not demonstrated (see Section 5.1 – Pharmacodynamic Properties, Clinical Trials, Paediatric and Adolescent Population and Section 5.2 - Pharmacokinetic Properties – Use in Paediatric and Adolescent Patients).

4.3 Contraindications

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

4.4 Special Warnings and Precautions for Use

Effects of Smoking Cessation

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

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

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 have occurred in patients being treated with varenicline. Patients and their families, friends or carers should be advised that the patient should stop taking VARENICLINE VIATRIS and contact a healthcare professional immediately if changes in behaviour or thinking, agitation or depressed mood that are not typical for the patient are observed, or if patient develops suicidal ideation or suicidal behaviour.

Doctors should discuss the efficacy and safety profile of VARENICLINE VIATRIS with patients attempting to quit smoking with VARENICLINE VIATRIS and advise them of the possible emergence of neuropsychiatric symptoms. Patients and their families, friends or carers should be alerted to the need to monitor for neuropsychiatric symptoms including changes in behaviour or thinking, anxiety, psychosis, mood swings, agitation, aggression, depressed mood, suicidal ideation and suicidal behaviour. Patients should be advised that alcohol intake may increase the risk of experiencing neuropsychiatric events during treatment with VARENICLINE VIATRIS.

Patients and their families, friends or carers should be encouraged to report any history of psychiatric illness prior to initiating treatment. There have been post-marketing reports of neuropsychiatric symptoms, some serious, as well as worsening of pre-existing psychiatric illness. A causal association between varenicline and these symptoms has not been established although association cannot be excluded. Some cases may have been complicated by the symptoms of nicotine withdrawal in patients who stopped smoking; however, some of these symptoms have occurred in patients who continued to smoke.

In many post-marketing cases, resolution of symptoms after discontinuation of varenicline was reported, although in some cases the symptoms persisted; therefore, ongoing follow up should be provided until symptoms resolve. Doctors and other healthcare professionals should continue to monitor patients for the development of neuropsychiatric symptoms.

Neuropsychiatric Study

See Section 5.1 – Pharmacodynamic Properties, Clinical Trials, Study in Patients with and without a History of Psychiatric Disorder and Section 4.8 – Adverse Effects (Undesirable Effects), Special Populations.

Meta-analysis

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, 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. The majority of patients in both the varenicline and placebo groups who reported suicidal ideation and/or behaviour on the C-SSRS during treatment period had a pre-dosing C-SSRS positive history (23 [82%]) and (17 [63%]) respectively. Few patients reported these events in the other three trials (4 varenicline, 3 placebo), which generally excluded individuals with a known psychiatric history.

Table 1. 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 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). Sixteen of the 18 trials generally excluded individuals with a history of neuropsychiatric disease. 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 2 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 hospitalisations and fatal and non-fatal self-harm, in patients treated with varenicline versus patients prescribed NRT or bupropion. One study looked at rates of suicide, self-harm and treated depression and the other three looked at neuropsychiatric events requiring hospitalisation or emergency room visit. 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 NRT 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). However, the power to detect differences in these two studies was limited, especially for rare events. 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).

Accidental Injury, Including While Driving or Operating Machinery

There have been post-marketing reports of traffic accidents, near-miss incidents in traffic, and other accidental injuries in patients taking varenicline. In some cases, the patients reported somnolence, dizziness, loss of consciousness (blackouts), seizures or difficulty concentrating.

Therefore, patients should be advised not to engage in potentially hazardous activities, such as driving or operating complex machinery, until they know how VARENICLINE VIATRIS may affect them.

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. Advise patients to discontinue VARENICLINE VIATRIS and immediately contact a healthcare provider if they experience a seizure while on treatment.

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 VIATRIS and contact a health care provider immediately (see Section 4.8 – Adverse effects (Undesirable Effects), Post-Marketing Experience).

Skin 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 (see Section 4.8 – Adverse Effects (Undesirable Effects), Post-Marketing Experience).

Cardiovascular Events

In a post-marketing randomised, controlled study of 703 patients with stable cardiovascular (CV) disease, deaths and serious CV events occurring over the 52 weeks of the study (treatment-emergent and non-treatment-emergent) were adjudicated by a blinded, independent committee. The following adjudicated treatment-emergent events (on-treatment or up to 30 days after treatment) occurred with a frequency ≥1% in either treatment group: nonfatal myocardial infarction (1.1% vs. 0.3% for varenicline and placebo, respectively), and hospitalisation for angina pectoris (0.6% vs. 1.1%). During non-treatment follow up to 52 weeks, adjudicated events with a frequency ≥1% included need for coronary revascularisation (2.0% vs. 0.6%), hospitalisation for angina pectoris (1.7% vs. 1.1%), and new diagnosis of peripheral vascular disease (PVD) or admission for a PVD procedure (1.4% vs. 0.6%). Some of the patients requiring coronary revascularisation underwent the procedure as part of management of nonfatal MI and hospitalisation for angina. Cardiovascular death occurred in 0.3% of patients in the varenicline arm and 0.6% of patients in the placebo arm over the course of the 52 week study.

In the above smoking cessation study in patients with stable CV disease and in a meta-analysis of 15 clinical trials, which included the smoking cessation trial of patients with stable CV disease, 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 cardiovascular disease. Patients should be advised to seek medical attention in the event of new or worsening cardiovascular symptoms or if they experience signs and symptoms of myocardial infarction or stroke. Patients with known cardiovascular disease require ongoing assessment and management of other risk factors for cardiovascular disease (see Section 5.1 – Pharmacodynamic Properties, Clinical Trials, Cardiovascular Disease Study).

Somnambulism

Cases of somnambulism have been reported in patients taking varenicline. Some cases described harmful behaviour to self, others, or property. Instruct patients to discontinue VARENICLINE VIATRIS and notify their healthcare provider if they experience somnambulism.

Use in the Elderly

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

Use in Paediatric and Adolescent Patients

Varenicline is not recommended for use in patients <19 years of age because its efficacy in this population was not demonstrated (see Section 5.1 – Pharmacodynamic Properties, Clinical Trials, Paediatric and Adolescent Population and Section 5.2 - Pharmacokinetic Properties – Use in Paediatric and Adolescent Patients).

Effects on Laboratory Tests

No data available.

4.5 Interactions with Other Medicines and Other Forms of Interactions

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

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

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

In vitro studies demonstrate that active renal secretion of varenicline tartrate is mediated by the human organic cation transporter, OCT2. Co-administration with inhibitors of OCT2 does not require a dose adjustment of VARENICLINE VIATRIS 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 - Pharmacokinetic Properties) and therefore a dose adjustment of VARENICLINE VIATRIS 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 – Special Warnings and Precautions for Use).

***Alcohol**:* There is 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. Drinking alcohol may increase the risk of experiencing neuropsychiatric events during treatment with VARENICLINE VIATRIS.

Use with Other Therapies for Smoking Cessation

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

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

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

4.6 Fertility, Pregnancy and Lactation

Effects on Fertility

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

Use in Pregnancy - Pregnancy Category B3

A moderate amount of data on pregnant women indicated no malformative or fetal/neonatal toxicity of varenicline (see Section 5.1 – Pharmacodynamic Properties). The use of VARENICLINE VIATRIS in pregnant women is not recommended.

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%).

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

In animal reproduction studies, varenicline has been shown to have adverse effects on the 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.

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

Use in Lactation

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

4.7 Effects on Ability to Drive and Use Machines

VARENICLINE VIATRIS may cause dizziness, sleepiness and loss of consciousness and therefore may influence the ability to drive or use machines. Patients are advised not to drive, operate complex machinery, or engage in other potentially hazardous activities until it is know whether this medicine affects their ability to perform these activities.

4.8 Adverse Effects (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.

Premarketing 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 3 includes the most frequently occurring adverse events 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 3 Treatment-emergent Adverse Events Reported in Studies at a Rate ≥1%

	Percentage of Patients Reporting Event	
	Varenicline	Placebo
	N=5823	N=4191
Infections and infestations		
Bronchitis	1.3	1.8
Gastroenteritis	1.1	1.0
Influenza	3.1	2.9
Nasopharyngitis	11.0	8.9
Sinusitis	1.6	1.7
Upper respiratory tract infection	6.4	7.6
Investigations		
Weight increased	2.2	1.1
Metabolism and Nutrition Disorders		
Increased appetite	3.5	2.3
Decreased appetite	1.8	1.6
Psychiatric Disorders		
Abnormal Dreams	10.0	4.0
Agitation	1.2	1.1
Anxiety	3.5	4.9
Depressed mood	1.6	1.5
Depression	2.1	2.3
Insomnia	12.0	7.4
Irritability	5.0	4.6
Middle insomnia	1.2	0.6
Nightmare	1.2	0.6
Restlessness	0.8	1.0
Sleep disorder	3.6	2.4
Nervous System Disorders		
Disturbance in attention	2.4	2.5
Dizziness	4.8	5.3
Dysgeusia	3.9	2.4
Headache	13.9	11.0
Somnolence	3.0	2.0
Respiratory, Thoracic and Mediastinal Disorders		

Table 3 Treatment-emergent Adverse Events Reported in Studies at a Rate ≥1%		
	Percentage of Patients Reporting Event	
	Varenicline	Placebo
	N=5823	N=4191
Cough	2.3	2.6
Dyspnoea	1.2	0.6
Oropharyngeal pain	1.8	1.5
Gastrointestinal Disorders		
Abdominal discomfort	1.5	1.0
Abdominal distension	1.8	0.9
Abdominal pain	1.8	1.2
Abdominal pain upper	3.1	1.7
Constipation	6.3	2.9
Diarrhoea	4.4	3.8
Dry mouth	3.8	2.9
Dyspepsia	4.3	2.4
Flatulence	4.1	2.1
Gastrooesophageal reflux disease	1.0	0.6
Nausea	28.2	9.6
Toothache	1.2	1.0
Vomiting	4.5	1.8
Skin and Subcutaneous Tissue Disorders		
Rash	1.4	1.2
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	1.9	1.5
Back pain	3.4	3.0
Myalgia	1.4	0.9
Pain in extremity	1.2	1.2
General Disorders and Administration Site Conditions		
Asthenia	1.0	0.6
Fatigue	5.0	4.1
Chest pain	1.1	0.9
Vascular Disorders		
Hypertension	1.2	1.1

In the listing below, all adverse reactions which occurred at a rate <1% are listed by system organ class and frequency (uncommon (≥1/1,000, <1/100) and rare (≥1/10,000 to <1/1,000)). This listing is based on treatment-emergent (during treatment and 30 days after last dose) all-causality AEs from the 19 placebo-controlled studies and takes into account the following factors:

- Event rates related to placebo rates
- Plausibility of a causal relationship based on pharmacokinetic/pharmacodynamics properties
- Specificity of the event such that it is informative, and
- Whether clusters of two or more similar events were best combined under a single term.

System Organ Class	
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
Eye Disorders	
Uncommon	Conjunctivitis, eye pain
Rare	Photophobia
Ear and Labyrinth Disorders	
Uncommon	Tinnitus
Cardiac Disorders	
Uncommon	Palpitations, angina pectoris, tachycardia, heart rate increased
Rare	Electrocardiogram T wave amplitude decreased, atrial fibrillation, electrocardiogram ST segment depression
Vascular Disorders	
Uncommon	Hot flush, blood pressure increased
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

System Organ Class	
Skin and Subcutaneous Tissue Disorders	
Uncommon	Erythema, acne, hyperhidrosis
Musculoskeletal, Connective Tissue and Bone 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. Safety analyses included all subjects who received at least one dose of the study drug (see Section 5.1 – Pharmacodynamic Properties, Clinical Trials and Section 4.4 – Special Warnings and Precautions for Use, Psychiatric Symptoms and Cardiovascular Events).

Patients With and Without a History of Psychiatric Disorder

Adverse events from the neuropsychiatric (NPS) safety study are presented in the following tables. There were more events reported in patients in the psychiatric cohort in each treatment group compared with the non-psychiatric cohort.

Table 4 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 and psychiatric cohorts.

Table 4 Composite NPS Adverse Event Primary End Point By Treatment Group								
	Non-psychiatric Cohort N=3984				Psychiatric Cohort N=4074			
	Varenicline 1 mg BID	Bupropion SR 150 mg BID	NRT patch* 21 mg/day with taper	Placebo	Varenicline 1 mg BID	Bupropion SR 150 mg BID	NRT patch* 21 mg/day with taper	Placebo
Number of patients treated	990	989	1066	999	1026	1017	1016	1015
Composite NPS AE Primary Endpoint, n (%)	13 (1.3)	22 (2.2)	25 (2.5)	24 (2.4)	67 (6.5)	68 (6.7)	53 (5.2)	50 (4.9)
RD (95% CI) vs. Placebo	-1.28 (-2.40, -0.15)	-0.08 (-1.37, 1.21)	-0.21 (-1.54, 1.12)	-	1.59 (-0.42, 3.59)	1.78 (-0.24, 3.81)	0.37 (-1.53, 2.26)	-
RD (95% CI) vs. NRT patch*	-1.07 (-2.21, 0.08)	0.13 (-1.19, 1.45)	-	-	1.22 (-0.81, 3.25)	1.42 (-0.63, 3.46)	-	-
RD (95% CI) vs. Bupropion	-1.19 (-2.30, -0.09)	-	-	-	-0.20 (-2.34, 1.95)	-	-	-

NPS AE Primary endpoint Components were: Anxiety, Depression, Feeling abnormal, Hostility, Agitation, Aggression, Delusions, Hallucinations, Homicidal ideation, Mania, Panic, Paranoia, Psychosis, Suicidal behaviour, Suicidal ideation, Completed suicide.
RD=risk difference. Differences were considered significant if their associated 95% CIs were entirely below or above zero.
* administered as monotherapy, 21 mg QD (weeks 1-8), 14 mg QD (weeks 8-10) and 7 mg QD (weeks 10-12).

In the non-psychiatric cohort, the composite endpoint 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 patch.

In the psychiatric cohort, the composite endpoint 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 patch.

The use of varenicline, bupropion and NRT patch in the non-psychiatric or 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 patch in the non-psychiatric or psychiatric cohort.

Based on the generalised linear regression model, the rate of the primary NPS AE endpoint was significantly higher in the psychiatric cohort compared to the non-psychiatric cohort ($p<0.0001$) for effect of the cohort in all treatment arms.

Table 5 Adverse Events in the Suicidal and Self-injurious Behaviours NEC High Level group Term – by Cohort, Safety Population				
High Level Group Term Preferred Term	**Number (%) of Subjects**			
	Varenicline	**Bupropion**	**NRT patch***	**Placebo**
Suicidal and self-injurious behaviours NEC				
Non-Psychiatric History	**N=990**	**N=989**	**N=1066**	**N=999**
Suicidal ideation	2 (0.2)[a]	2 (0.2)[b]	2 (0.2)	3 (0.3)
Suicide attempt	0	1 (0.1)	1 (0.1)	0
Completed suicide	0	0	0	1 (0.1)
Psychiatric History	**N=1026**	**N=1017**	**N=1016**	**N=1015**
Suicidal ideation	8 (0.8)[c]	3 (0.3)[b]	6 (0.6)[c]	7 (0.7)[d]
Suicidal behaviour	0	0	0	1 (0.1)[b]
Suicide attempt	0	1 (0.1)	0	1 (0.1)

[a] 2 events rated as mild
[b] 1 event rated as mild
[c] 3 events rated as mild
[d] 5 events rated as mild
N=total number of subjects per treatment group; NEC=not elsewhere classified; NRT=nicotine replacement therapy
* administered as monotherapy, 21 mg QD (weeks 1-8), 14 mg QD (weeks 8-10) and 7 mg QD (weeks 10-12).

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).

Table 6 Most Frequently Reported All-Causality Treatment - Emergent Adverse Events (≥ 5% of Subjects in any Treatment Group) — Both Cohorts, Safety Population

System Organ Class	Non-Psychiatric History			
Preferred Term	**Varenicline (N=990)**	**Bupropion (N=989)**	**NRT patch* (N=1006)**	**Placebo (N=999)**
Subjects with Adverse Events	720 (72.7)	704 (71.2)	698 (69.4)	649 (65.0)
Gastrointestinal Disorders	379 (38.3)	234 (23.7)	233 (23.2)	190 (19.0)
Nausea	243 (24.5)	90 (9.1)	95 (9.4)	63 (6.3)
Dry mouth	29 (2.9)	70 (7.1)	31 (3.1)	26 (2.6)
General Disorders and Administration Site Conditions	110 (11.1)	110 (11.1)	191 (19.0)	94 (9.4)
Application site pruritus	11(1.1)	6 (0.6)	51 (5.1)	11(1.1)
Infections and Infestations	263 (26.6)	241 (24.4)	240 (23.9)	254 (25.4)
Nasopharyngitis	86 (8.7)	79 (8.0)	65 (6.5)	73 (7.3)
Upper respiratory tract infection	47 (4.7)	48 (4.9)	40 (4.0)	55 (5.5)
Nervous System Disorders	206 (20.8)	199 (20.1)	225 (22.4)	162 (16.2)
Headache	116 (11.7)	87 (8.8)	129 (12.8)	95 (9.5)
Dizziness	33 (3.3)	51 (5.2)	38 (3.8)	28 (2.8)
Psychiatric Disorders	315 (31.8)	332 (33.6)	301 (29.9)	259 (25.9)
Anxiety	46 (4.6)	64 (6.5)	45 (4.5)	57 (5.7)
Abnormal dreams	83 (8.4)	47 (4.8)	111 (11.0)	39 (3.9)
Insomnia	95 (9.6)	126 (12.7)	91 (9.0)	73 (7.3)
Gastrointestinal Disorders	407 (39.7)	293 (28.8)	247 (24.3)	224 (22.1)
Nausea	268 (26.1)	111 (10.9)	104 (10.2)	74 (7.3)
Dry mouth	37 (3.6)	76 (7.5)	28 (2.8)	38 (3.7)
General Disorders and Administration Site Conditions	160 (15.6)	131 (12.9)	213 (21.0)	135 (13.3)
Application site pruritus	11 (1.1)	6 (0.6)	58 (5.7)	5 (0.5)
Fatigue	85 (8.3)	37 (3.6)	47 (4.6)	59 (5.8)
Infections and Infestations	270 (26.3)	234 (23.0)	254 (25.0)	252 (24.8)
Nasopharyngitis	88 (8.6)	77 (7.6)	61 (6.0)	62 (6.1)
Upper respiratory tract infection	62 (6.0)	56 (5.5)	57 (5.6)	60 (5.9)
Nervous System Disorders	234 (22.8)	241 (23.7)	218 (21.5)	212 (20.9)
Headache	129 (12.6)	99 (9.7)	104 (10.2)	104 (10.2)
Psychiatric Disorders	405 (39.5)	435 (42.8)	420 (41.3)	354 (34.9)
Agitation	47 (4.6)	56 (5.5)	39 (3.8)	41 (4.0)
Anxiety	86 (8.4)	105 (10.3)	93 (9.2)	63 (6.2)
Depressed mood	47 (4.6)	47 (4.6)	52 (5.1)	52 (5.1)
Irritability	48 (4.7)	42 (4.1)	61 (6.0)	67 (6.6)
Abnormal dreams	118 (11.5)	84 (8.3)	140 (13.8)	53 (5.2)
Insomnia	94 (9.2)	119 (11.7)	104 (10.2)	66 (6.5)

N=total number of subjects per treatment group; NRT=nicotine replacement therapy.
Subjects are only counted once per treatment for each row.
Treatment-emergent includes the interval from first date of study drug to last date of study drug plus 30 days.
* administered as monotherapy, 21 mg QD (weeks 1-8), 14 mg QD (weeks 8-10) and 7 mg QD (weeks 10-12).

A cardiovascular safety assessment of this study (N=8,058) showed no statically significant difference in the primary cardiovascular endpoint of time to major adverse cardiovascular event (MACE), defined as cardiovascular death, non-fatal myocardial infarction or non-fatal stroke between treatment groups during the treatment phase. The total number of MACE events reported during this study and through a 28-week observational extension of this study (N=4,595) in which no subjects received study treatment, was low with 3 (0.15%) subjects given varenicline reporting such events, 9 (0.45%) subjects given bupropion, 6 (0.3%) subjects given nicotine replacement therapy and 8 (0.4%) subjects given placebo. Due to the relatively low number of MACE events overall, an association between varenicline and increased risk of cardiovascular outcomes cannot be entirely excluded. Of all treated subjects, 1,749 (21.7%) had a medium CV risk and 644 (8.0%) had a high CV risk, as defined by Framingham score at baseline.

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 .There are a number of confounding factors which may have contributed, including effects of nicotine withdrawal due to partial or complete smoking discontinuation; concomitant, or history of psychiatric conditions; and the concomitant use of other CNS drugs and/or alcohol. In many post-marketing cases, resolution of symptoms after discontinuation of varenicline was reported, although in some cases the symptoms persisted; therefore, ongoing follow up should be provided until symptoms resolve. 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 – Special Warnings and Precautions for Use).

There have also been reports of hypersensitivity reactions, such as angioedema and of rare but severe cutaneous reactions, including Stevens – Johnson Syndrome and Erythema Multiforme in patients taking varenicline (see Section 4.4 – Special Warnings and Precautions for Use).

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 been reports of somnambulism, some resulting in harmful behaviour to self, others, or property, in patients treated with varenicline.

There have been post-marketing reports of traffic accidents, near-miss incidents in traffic, and other accidental injuries in patients taking varenicline. In some cases,

the patients reported somnolence, dizziness, loss of consciousness (blackouts), seizures or difficulty concentrating. There have also been post-marketing reports of diabetes mellitus, hyperglycaemia and convulsions.

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

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 dialysed in patients with end stage renal disease (see Section 5.2 - Pharmacokinetic Properties); however, there is no experience in dialysis following overdose.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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

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

Clinical Trials

The efficacy of varenicline in smoking cessation was demonstrated in three pre-marketing clinical trials in which a total of 2,619 chronic cigarette smokers (≥10 cigarettes per day) received varenicline. Two of these studies were double-blind comparisons between varenicline, bupropion and placebo, assessing critical aspects of smoking cessation,

including end-of- treatment and long-term abstinence rates after 12 weeks of treatment. In addition, the effects on reducing craving and withdrawal that can occur during smoking cessation and the reinforcing effects that can perpetuate smoking behaviour were studied. The third study assessed the effect of an additional 12 weeks of treatment on maintaining long-term abstinence.

Comparative Clinical Studies

Two identical double-blind clinical trials prospectively compared the efficacy of 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), 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.

Patient Reported Craving, Withdrawal and Reinforcing Effects of Smoking

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.

Across both Studies 1 and 2, 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.

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 patients. Patients 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 patients received varenicline and 165 received placebo. Patients 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. Patients 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 patients 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 summarised in the following table:

Table 9 Rates of CO-confirmed abstinence for Flexible 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
			P<0.0001

Re-treatment with Varenicline Study

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

Cardiovascular Disease Study

Varenicline was evaluated in a randomised, double-blind, placebo-controlled study of 703 patients with stable, documented cardiovascular disease (other than or in addition to hypertension) that had been diagnosed for more than 2 months. Patients 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. Patients treated with varenicline had a superior rate of CO-confirmed abstinence during weeks 9 through 12 (47.3 %) compared to patients 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 patients treated with placebo (7.4%) (odds ratio 3.19; 95% CI 1.97, 5.18; p<0.0001).

The key results are summarised in the following table:

Table 11 Rates of CO-confirmed abstinence for Patients 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

Chronic Obstructive Pulmonary Disease (COPD) Study

Varenicline was evaluated in a randomised, double-blind, placebo-controlled study of patients aged ≥ 35 years with mild-to-moderate COPD with post-bronchodilator FEV_1/FVC <70% and FEV_1 ≥ 50% of predicted normal value. Patients were randomised to varenicline 1 mg twice daily (N=223) or placebo (N=237) for a treatment of 12 weeks and then were followed for 40 weeks post-treatment. Patients treated with varenicline had a superior rate of CO-confirmed abstinence during weeks 9 through 12 (41.7%) compared to patients treated with placebo (9.3%) and from week 9 through 52 (19.7%) compared to patients treated with placebo (5.9%).

The key results are summarised in the following table:

Table 12 Rates of CO-confirmed abstinence for Patients with Chronic Obstructive Pulmonary Disease

	Varenicline n=223	Placebo n=237	Odds ratio (95% CI), p value
CA wk 9-12	41.7%	9.3%	7.65 (4.51, 12.97) p<0.0001
CA wk 9-52	19.7%	5.9%	4.19 (2.19, 8.00) p<0.0001

Major Depressive Disorder (MDD) Study

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.

The key efficacy results are summarised in the following table:

Table 13 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

Stable Schizophrenia or Schizoaffective Disorder Study

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 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.

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 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 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 key results are summarised in the following table:

Table 14 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

Neuropsychiatric Safety Study in Patients 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 (NRT) patch 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.

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 population of this study were nausea (25.3% vs. 6.8% on placebo), headache (12.2% vs. 9.9% on placebo) and abnormal dreams (10% vs. 4.6% on placebo) (see Section 4.8 – Adverse Effects (Undesirable Effects), 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, NRT patch and placebo.

The key efficacy results are summarised 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 patch*	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 patch* 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 patch*	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 patch*	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 patch* 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 patch*	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

* administered as monotherapy, 21 mg QD (weeks 1-8), 14 mg QD (weeks 8-10) and 7 mg QD (weeks 10-12).

Paediatric and Adolescent 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. The varenicline safety profile in this study was consistent with that shown in adult studies. (See Section 4.2 – Dose and Method of Administration, Use in Paediatric and Adolescent Patients and Section 5.2 - Pharmacokinetic Properties, Use in Paediatric and Adolescent Patients).

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 twice daily. 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 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 – Dose and Method of Administration). Dosing should begin at 0.5 mg once daily for the first 3 days, and then increase to 1 mg once daily.

Elderly (>65 years)

No dosage adjustment is necessary for elderly patients (see Section 4.2 – Dose and Method of Administration).

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

Use in Paediatric and Adolescent Patients

Varenicline is not recommended for use in patients under 19 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 – Dose and Method of Administration, Use in Paediatric and Adolescent Patients and Section 5.1 – Pharmcodynamic Properties, Clinical Trials, Paediatric and Adolescent 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 (Cmax) up to 130 and 50 times the human plasma Cmax 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 Cmax (incidence 1/65 rats) and 50 times the human Cmax (incidence 2/65 rats); the no-effect exposure was 10 times the human Cmax. 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Ascorbic acid
Microcrystalline cellulose
Calcium hydrogen phosphate
Croscarmellose sodium
Silica–colloidal anhydrous
Magnesium stearate

Film coating

0.5 mg Tablet
Hypromellose
Titanium dioxide
Macrogol 400

1 mg Tablet
Hypromellose
Titanium dioxide
Macrogol 400
FD&C blue #2 Aluminium Lake

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf Life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special Precautions for Storage

Store below 25°C.

6.5 Nature and Contents of Container

VARENICLINE VIATRIS tablets are presented in Alu/Alu blisters (a 45 µm OPA complex foil (Polyamide/Aluminium/PVC) blister heatsealed with 20 µm aluminium foil) , or round white high-density polyethylene (HDPE) bottles with a child-resistant cap (CRC) and one dessicant cannister in the following pack sizes (not all presentations marketed):

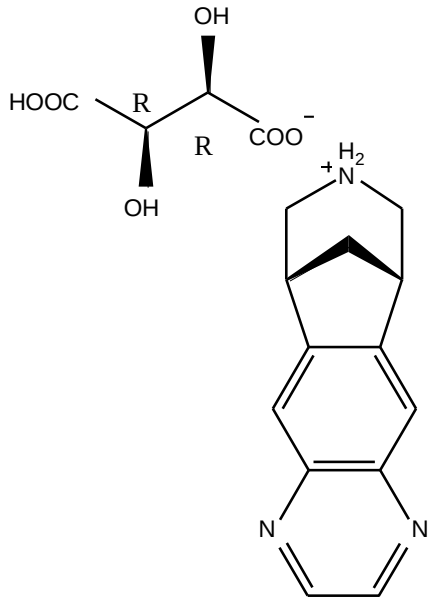
- Initiation Pack containing 11 x 0.5 mg tablets and 42 x 1 mg tablets in blisters within a secondary heat sealed wallet.
- Maintenance Pack comprising of one bottle containing 56 x 1 mg tablets.

6.6 Special Precautions for Disposal

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physicochemical Properties

Chemical Structure



Varenicline tartrate powder is a white to off-white to slightly yellow solid. It is highly soluble in water. The pKa (ionisation constant) for varenicline is 9.2. The octanol-water partition coefficient (Log D) of varenicline tartrate is -1.23 at pH 5, -0.817 at pH 7 and 0.758 at pH 9.

Chemical name: 7,8,9,10–tetrahydro-6,10-methano-6*H*-pyrazino [2,3-h] [3] benzazepine, (2*R*, 3*R*)-2,3-dihydroxybutanedioate (1:1).

Molecular weight: 361.35 Daltons.

Molecular formula: $C_{13}H_{13}N_3 \bullet C_4H_6O_6$.

CAS Number

CAS Registry No: 375815-87-5.

7. MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (S4).

8. SPONSOR

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9. DATE OF FIRST APPROVAL

16 November 2023

10. DATE OF REVISION

xx-xxxxx-xxxx

Summary Table of Changes

Section changed	Summary of new information
-	-