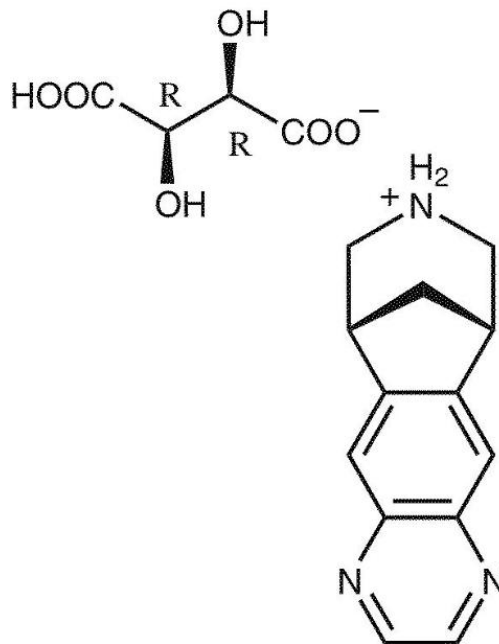


SmokeLESS Full Prescribing Information

DESCRIPTION

SmokeLESS tablets contain the active ingredient, varenicline (as the tartrate salt), which is a partial agonist selective for (alpha)₄(beta)₂ nicotinic acetylcholine receptor subtypes. *Varenicline*, as the tartrate salt, is a powder which is a white to off-white to slightly yellow solid with the following chemical name: 7,8,9,10-tetrahydro-6,10-methano-6H-pyrazino[2,3-h][3]benzazepine,(2*R*,3*R*)-2,3-dihydroxybutanedioate (1:1). It is highly soluble in water.

Varenicline tartrate has a molecular weight of 361.35 Daltons, and a molecular formula of C₁₃H₁₃N₃ · C₄H₆O₆. The chemical structure is:





SmokeLESS is supplied for oral administration in two strengths: a 0.5 mg coated tablet and a 1 mg coated tablet.

CLINICAL PHARMACOLOGY

Mechanism Of Action

- Varenicline binds with high affinity and selectivity at $(\alpha)_4(\beta)_2$ neuronal nicotinic acetylcholine receptors.

The efficacy of **SmokeLESS** in smoking cessation is believed to be the result of varenicline's activity at a sub-type of the nicotinic receptor where its binding produces agonist activity, while simultaneously preventing nicotine binding to $(\alpha)_4(\beta)_2$ receptors.

- Electrophysiology studies *in vitro* and neurochemical studies *in vivo* have shown that varenicline binds to $(\alpha)_4(\beta)_2$ neuronal nicotinic acetylcholine receptors and stimulates receptor-mediated activity, but at a significantly lower level than nicotine.

Varenicline blocks the ability of nicotine to activate $(\alpha)_4(\beta)_2$ receptors and thus to stimulate the central nervous mesolimbic dopamine system, believed to be the neuronal mechanism underlying reinforcement and reward experienced upon smoking.

Varenicline is highly selective and binds more potently to $(\alpha)_4(\beta)_2$ receptors than to other common nicotinic receptors (>500-fold $(\alpha)_3(\beta)_4$, >3500-fold $(\alpha)_7$, >20,000-fold $(\alpha)_1(\beta)(\gamma)$ [dgr]), or to non-nicotinic receptors and transporters (>2000-fold).

Varenicline also binds with moderate affinity ($K_i = 350$ nM) to the 5-HT₃ receptor.

Pharmacokinetics

Absorption/Distribution

Maximum plasma concentrations of varenicline occur typically within 3-4 hours after oral administration.

Following administration of multiple oral doses of varenicline, steady-state conditions were reached within 4 days.

Over the recommended dosing range, varenicline exhibits linear pharmacokinetics after single or repeated doses.



In a mass balance study, absorption of varenicline was virtually complete after oral administration and systemic availability was high.

Oral bioavailability of varenicline is unaffected by food or time-of-day dosing.

Plasma protein binding of varenicline is low ($\leq 20\%$) and independent of both age and renal function.

Metabolism/Elimination

The elimination half-life of varenicline is approximately 24 hours.

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

Renal elimination of varenicline is primarily through glomerular filtration along with active tubular secretion possibly via the organic cation transporter, OCT2.

Pharmacokinetics In Special Patient Populations

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

Renal impairment

Varenicline pharmacokinetics were unchanged in subjects with mild renal impairment (estimated creatinine clearance >50 mL/min and ≤ 80 mL/min).

In patients with moderate renal impairment (estimated creatinine clearance ≥ 30 mL/min and ≤ 50 mL/min), varenicline exposure increased 1.5-fold compared with subjects with normal renal function (estimated creatinine clearance >80 mL/min).

In subjects with severe renal impairment (estimated creatinine clearance <30 mL/min), varenicline exposure was increased 2.1-fold.

In subjects with end-stage-renal disease (ESRD) undergoing a three hour session of hemodialysis for three days a week, varenicline exposure was increased 2.7-fold following 0.5 mg once daily administration for 12 days.

The plasma C_{max} and AUC of varenicline noted in this setting were similar to healthy subjects receiving about 1 mg twice daily.

Caution is warranted with the use of **SmokeLESS** in subjects with renal impairment.





Additionally, in subjects with ESRD, varenicline was efficiently removed by hemodialysis.

Geriatric

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

Pediatric

- Because the safety and effectiveness of **SmokeLESS** in pediatric patients have not been established, **SmokeLESS** is not recommended for use in patients under 18 years of age.

- When 22 pediatric patients aged 12 to 17 years (inclusive) received a single 0.5 mg and 1 mg-dose of varenicline, the pharmacokinetics of varenicline was approximately dose proportional between the 0.5 mg and 1 mg doses.

Systemic exposure, as assessed by AUC(0-∞), and renal clearance of varenicline were comparable to those of an adult population.

Hepatic impairment

Due to the absence of significant hepatic metabolism, varenicline pharmacokinetics should be unaffected in patients with hepatic insufficiency.

Drug-Drug Interactions

- Drug interaction studies were performed with varenicline and digoxin, warfarin, transdermal nicotine, bupropion, cimetidine and metformin.

No clinically meaningful pharmacokinetic drug-drug interactions have been identified.

- *In vitro* studies demonstrated that varenicline does not inhibit the following cytochrome P450 enzymes (IC50 >6400 ng/mL): 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4/5.



Also, in human hepatocytes *in vitro*, varenicline does not induce the cytochrome P450 enzymes 1A2 and 3A4.

- *In vitro* studies demonstrated that varenicline does not inhibit human renal transport proteins at therapeutic concentrations.

Therefore, drugs that are cleared by renal secretion (e.g. metformin) are unlikely to be affected by varenicline.

- *In vitro* studies demonstrated the active renal secretion of varenicline is mediated by the human organic cation transporter, OCT2.

Co-administration with inhibitors of OCT2 may not require a dose adjustment of **SmokeLESS** as the increase in systemic exposure to **SmokeLESS** is not expected to be clinically meaningful.

Furthermore, since metabolism of varenicline represents less than 10% of its clearance, drugs known to affect the cytochrome P450 system are unlikely to alter the pharmacokinetics of **SmokeLESS** and therefore a dose adjustment of **SmokeLESS** would not be required.

Metformin: When co-administered to 30 smokers varenicline (1 mg BID) did not alter the steady-state pharmacokinetics of metformin (500 mg BID), which is a substrate of OCT2.

Metformin had no effect on varenicline steady-state pharmacokinetics.

Cimetidine: Co-administration of an OCT2 inhibitor, cimetidine (300 mg QID), with varenicline (2 mg single dose) to 12 smokers increased the systemic exposure of varenicline by 29% (90% CI: 21.5%, 36.9%) due to a reduction in varenicline renal clearance.

Digoxin: Varenicline (1 mg BID) did not alter the steady-state pharmacokinetics of digoxin administered as a 0.25 mg daily dose in 18 smokers.



Warfarin: Varenicline (1 mg BID) did not alter the pharmacokinetics of a single 25 mg dose of (R, S)-warfarin in 24 smokers.

Prothrombin time (INR) was not affected by varenicline.

Smoking cessation itself may result in changes to warfarin pharmacokinetics.

Use with other therapies for smoking cessation:

Bupropion: Varenicline (1 mg BID) did not alter the steady-state pharmacokinetics of bupropion (150 mg BID) in 46 smokers.

The safety of the combination of bupropion and varenicline has not been established.

Nicotine replacement therapy (NRT): Although co-administration of varenicline (1 mg BID) and transdermal nicotine (21 mg/day) for up to 12 days did not affect nicotine pharmacokinetics, the incidence of nausea, headache, vomiting, dizziness, dyspepsia and fatigue was greater for the combination than for NRT alone.

In this study, eight of twenty-two (36%) subjects treated with the combination of varenicline and NRT prematurely discontinued treatment due to adverse events, compared to 1 of 17 (6%) of subjects treated with NRT and placebo.

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





CLINICAL STUDIES

- The efficacy of Varenicline (the active ingredient of **SmokeLESS**) in smoking cessation was demonstrated in six clinical trials in which a total of 3659 chronic cigarette smokers (≥ 10 cigarettes per day) were treated with Varenicline.

In all clinical studies, abstinence from smoking was determined by patient self-report and verified by measurement of exhaled carbon monoxide ($\text{CO} \leq 10$ ppm) at weekly visits.

Among the Varenicline treated patients enrolled in these studies, the completion rate was 65%.

Except for the initial Phase 2 study (Study 1) and the maintenance of abstinence study (Study 6), patients were treated for 12 weeks and then were followed for 40 weeks post-treatment.

Most subjects enrolled in these trials were white (79% - 96%).

All studies enrolled almost equal numbers of men and women.

The average age of subjects in these studies was 43 years.

Subjects on average had smoked about 21 cigarettes per day for an average of approximately 25 years.

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

Initiation of Abstinence

- Study 1: This was a six-week dose-ranging study comparing Varenicline to placebo. This study provided initial evidence that Varenicline at a total dose of 1 mg per day or 2 mg per day was effective as an aid to smoking cessation.

- Study 2: This study of 627 subjects compared Varenicline 1 mg per day and 2 mg per day with placebo.

Patients were treated for 12 weeks (including one week titration) and then were followed for 40 weeks post-treatment.





Varenicline was given in two divided doses.

Each dose of Varenicline was given in two different regimens, with and without initial dose titration, to explore the effect of different dosing regimens on tolerability.

For the titrated groups, dosage was titrated up over the course of one week, with full dosage achieved starting with the second week of dosing.

The titrated and nontitrated groups were pooled for efficacy analysis.

- Forty five percent of subjects receiving Varenicline 1 mg per day (0.5 mg BID) and 51% of subjects receiving 2 mg per day (1 mg BID) had CO-confirmed continuous abstinence during weeks 9 through 12 compared to 12% of subjects in the placebo group.

In addition, 31% of the 1 mg per day group and 31% of the 2 mg per day group were continuously abstinent from one week after TQD through the end of treatment as compared to 8% of the placebo group.

- Study 3: This flexible-dosing study of 312 subjects examined the effect of a patient-directed dosing strategy of Varenicline or placebo.

After an initial one-week titration to a dose of 0.5 mg BID, subjects could adjust their dosage as often as they wished between 0.5 mg QD to 1 mg BID per day.

Sixty nine percent of patients titrated to the maximum allowable dose at any time during the study.

For 44% of patients, the modal dose selected was 1 mg BID; for slightly over half of the study participants, the modal dose selected was 1 mg/day or less.

- Of the subjects treated with Varenicline, 40% had CO-confirmed continuous abstinence during weeks 9 through 12 compared to 12% in the placebo group.

In addition, 29% of the Varenicline group were continuously abstinent from one week after TQD through the end of treatment as compared to 9% of the placebo group.

- Study 4 and Study 5: These identical double-blind studies compared Varenicline 2 mg per day, bupropion sustained release (SR) 150 mg BID, and placebo.

Patients were treated for 12 weeks and then were followed for 40 weeks post-treatment.





The Varenicline dosage of 1 mg BID was achieved using a titration of 0.5 mg QD for the initial 3 days followed by 0.5 mg BID for the next 4 days.

The bupropion SR dosage of 150 mg BID was achieved using a 3-day titration of 150 mg QD.

Study 4 enrolled 1022 subjects and Study 5 enrolled 1023 subjects.

Patients inappropriate for bupropion treatment or patients who had previously used bupropion were excluded.

- In Study 4, subjects treated with Varenicline had a superior rate of CO-confirmed abstinence during weeks 9 through 12 (44%) compared to patients treated with bupropion SR (30%) or placebo (17%).

The bupropion SR quit rate was also superior to placebo.

In addition, 29% of the Varenicline group were continuously abstinent from one week after TQD through the end of treatment as compared to 12% of the placebo group and 23% of the bupropion SR group.

- Similarly in Study 5, subjects treated with Varenicline had a superior rate of CO-confirmed abstinence during weeks 9 through 12 (44%) compared to patients treated with bupropion SR (30%) or placebo (18%).

The bupropion SR quit rate was also superior to placebo.

In addition, 29% of the Varenicline group were continuously abstinent from one week after TQD through the end of treatment as compared to 11% of the placebo group and 21% of the bupropion SR group.



Table 1: Continuous Abstinence, Week 9 through 12 (95% confidence interval) across different studies

	Varenicline 0.5 mg BID	Varenicline 1 mg BID	Varenicline Flexible	Bupropion SR	Placebo
Study 2	45% (39%, 51%)	51% (44%, 57%)			12% (6%, 18%)
Study 3			40% (32%, 48%)		12% (7%, 17%)
Study 4		44% (38%, 49%)		30% (25%, 35%)	17% (13%, 22%)
Study 5		44% (38%, 49%)		30% (25%, 35%)	18% (14%, 22%)

Urge To Smoke

Based on responses to the Brief Questionnaire of Smoking Urges and the Minnesota Nicotine Withdrawal scale “Urge to Smoke” item, Varenicline reduced urge to smoke compared to placebo in all studies.

Long-Term Abstinence

Studies 1 through 5 included 40 weeks of post-treatment follow-up. In each study, Varenicline treated patients were more likely to maintain abstinence throughout the follow-up period than were patients treated with placebo (Table 2).

Table 2: Continuous Abstinence, Weeks 9 through 52 (95% confidence interval) across different studies



	Varenicline 0.5 mg BID	Varenicline 1 mg BID	Varenicline Flexible	Bupropion SR	Placebo
Study 2	19% (14%, 24%)	23% (18%, 28%)			4% (1%, 8%)
Study 3			22% (16%, 29%)		8% (3%, 12%)
Study 4		21% (17%, 26%)		16% (12%, 20%)	8% (5%, 11%)
Study 5		22% (17%, 26%)		14% (11%, 18%)	10% (7%, 13%)

- Study 6: This study assessed the effect of an additional 12 weeks of Varenicline therapy on the likelihood of long-term abstinence.

Patients in this study (n=1927) were treated with open-label Varenicline 1 mg BID for 12 weeks.

Patients who had stopped smoking by Week 12 were then randomized to double-blind treatment with Varenicline (1 mg BID) or placebo for an additional 12 weeks and then followed for 28 weeks post-treatment.

- The continuous abstinence rate from Week 13 through Week 24 was higher for subjects continuing treatment with Varenicline (70%) than for subjects switching to placebo (50%).

Superiority to placebo was also maintained during 28 weeks post-treatment follow-up (Varenicline 54% versus placebo 39%).

INDICATIONS AND USAGE

SmokeLESS is indicated as an aid to smoking cessation treatment.

WARNINGS

Neuropsychiatric Symptoms



Serious neuropsychiatric symptoms have occurred in patients being treated with Varenicline.

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.

All patients being treated with **SmokeLESS** should be observed for neuropsychiatric symptoms including changes in behavior, agitation, depressed mood, suicidal ideation and suicidal behavior.

These symptoms, as well as worsening of pre-existing psychiatric illness, have been reported in patients attempting to quit smoking while taking varenicline in the post-marketing experience.

Patients with serious psychiatric illness such as schizophrenia, bipolar disorder, and major depressive disorder did not participate in the pre-marketing studies of varenicline and the safety and efficacy of varenicline in such patients has not been established. Advise patients and caregivers that the patient should stop taking **SmokeLESS** and contact a health care provider immediately if agitation, depressed mood, or changes in behavior that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behavior.

PRECAUTIONS

General

Nausea was the most common adverse event associated with **SmokeLESS** treatment. Nausea was generally described as mild or moderate and often transient; however, for some subjects, it was persistent over several months.

The incidence of nausea was dose-dependent.

Initial dose-titration was beneficial in reducing the occurrence of nausea.

Nausea was reported by approximately 30% of patients treated with **SmokeLESS** 1 mg BID after an initial week of dose titration.

In patients taking **SmokeLESS** 0.5 mg BID, the incidence of nausea was 16% following initial titration.

Approximately 3% of subjects treated with **SmokeLESS** 1 mg BID in studies involving 12 weeks of treatment discontinued treatment prematurely because of nausea.





For patients with intolerable nausea, dose reduction should be considered.

Effect of smoking cessation: Physiological changes resulting from smoking cessation, with or without treatment with **SmokeLESS**, may alter the pharmacokinetics or pharmacodynamics of some drugs, for which dosage adjustment may be necessary (examples include theophylline, warfarin and insulin).

Drug Interactions

Based on varenicline characteristics and clinical experience to date, **SmokeLESS** has no clinically meaningful pharmacokinetic drug interactions.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Lifetime carcinogenicity studies were performed in CD-1 mice and Sprague-Dawley rats.

There was no evidence of a carcinogenic effect in mice administered varenicline by oral gavage for 2 years at doses up to 20 mg/kg/day (47 times the maximum recommended human daily exposure based on AUC).

Rats were administered varenicline (1, 5, and 15 mg/kg/day) by oral gavage for 2 years. In male rats (n = 65 per sex per dose group), incidences of hibernoma (tumor of the brown fat) were increased at the mid dose (1 tumor, 5 mg/kg/day, 23 times the maximum recommended human daily exposure based on AUC) and maximum dose (2 tumors, 15 mg/kg/day, 67 times the maximum recommended human daily exposure based on AUC). The clinical relevance of this finding to humans has not been established.

There was no evidence of carcinogenicity in female rats.

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



Impairment of fertility: There was no evidence of impairment of fertility in either male or female Sprague-Dawley rats administered varenicline succinate up to 15 mg/kg/day (67 and 36 times, respectively, the maximum recommended human daily exposure based on AUC at 1 mg BID).

However, a decrease in fertility was noted in the offspring of pregnant rats who were administered varenicline succinate at an oral dose of 15 mg/kg/day (36 times the maximum recommended human daily exposure based on AUC at 1 mg BID).

This decrease in fertility in the offspring of treated female rats was not evident at an oral dose of 3 mg/kg/day (9 times the maximum recommended human daily exposure based on AUC at 1 mg BID).

Pregnancy

Pregnancy Category C.

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

Nonteratogenic effects

- Varenicline succinate has been shown to have an adverse effect on the fetus in animal reproduction studies.

Administration of varenicline succinate to pregnant rabbits resulted in reduced fetal weights at an oral dose of 30 mg/kg/day (50 times the human AUC at 1 mg BID); this reduction was not evident following treatment with 10 mg/kg/day (23 times the maximum recommended daily human exposure based on AUC).

In addition, in the offspring of pregnant rats treated with varenicline succinate there were decreases in fertility and increases in auditory startle response at an oral dose of 15 mg/kg/day (36 times the maximum recommended human daily exposure based on AUC at 1 mg BID).

- There are no adequate and well-controlled studies in pregnant women.

SmokeLESS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.



Nursing mothers

Although it is not known whether this drug is excreted in human milk, animal studies have demonstrated that varenicline can be transferred to nursing pups.

Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from **SmokeLESS**, 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.

Labor and delivery

The potential effects of **SmokeLESS** on labor and delivery are not known.

Pediatric Use

Safety and effectiveness of **SmokeLESS** in pediatric patients have not been established; therefore, **SmokeLESS** is not recommended for use in patients under 18 years of age.

Geriatric Use

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

No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

- Varenicline is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function.

Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

- No dosage adjustment is recommended for elderly patients.



Information for Patients

- Patients should be instructed to set a date to quit smoking and to initiate **SmokeLESS** treatment one week before the quit date.
- Patients should be advised that **SmokeLESS** should be taken after eating, and with a full glass of water.
- Patients should be instructed how to titrate **SmokeLESS**, beginning at a dose of 0.5 mg/day.

Prescribers should explain that one 0.5 mg tablet should be taken daily for the first three days, and that for the next four days, one 0.5 mg tablet should be taken in the morning and one 0.5 mg tablet should be taken in the evening.

- Patients should be advised that, after the first seven days, the dose should be increased to one 1 mg tablet in the morning and one 1 mg tablet in the evening.
- Patients should be encouraged to continue to attempt to quit if they have early lapses after quit day.
- Patients should be informed that nausea and insomnia are side effects of **SmokeLESS** and are usually transient; however, patients should be advised that if they are persistently troubled by these symptoms, they should notify the prescribing physician so that a dose reduction can be considered.
- Patients should also be provided with educational materials and necessary counseling to support an attempt at quitting smoking.
- Patients should be informed that some medications may require dose adjustment after quitting smoking.
- Patients intending to become pregnant or planning to breast-feed an infant should be advised of the risks of smoking and risks and benefits of smoking cessation with **SmokeLESS**.
- Patients should be advised to use caution driving or operating machinery until they know how quitting smoking and/or varenicline may affect them.

ADVERSE REACTIONS

- During the premarketing development of Varenicline, over 4500 individuals were exposed to Varenicline, with over 450 treated for at least 24 weeks and approximately 100 for a year.





Most study participants were treated for 12 weeks or less.

- In Phase 2 and 3 placebo-controlled studies, the treatment discontinuation rate due to adverse events in patients dosed with 1 mg BID was 12% for Varenicline compared to 10% for placebo in studies of three months' treatment.

In this group, the discontinuation rates for the most common adverse events in Varenicline treated patients were as follows: nausea (3% vs. 0.5% for placebo), headache (0.6% vs. 0.9% for placebo), insomnia (1.2% vs. 1.1% for placebo), and abnormal dreams (0.3% vs. 0.2% for placebo).

Adverse Events were categorized using the Medical Dictionary for Regulatory Activities (MedDRA, Version 7.1).

- The most common adverse events associated with Varenicline (>5% and twice the rate seen in placebo-treated patients) were nausea, sleep disturbance, constipation, flatulence, and vomiting.

- Smoking cessation, with or without treatment, is associated with nicotine withdrawal symptoms and has also been associated with the exacerbation of underlying psychiatric illness.

- The most common adverse event associated with Varenicline treatment is nausea. For patients treated to the maximum recommended dose of 1 mg BID following initial dosage titration, the incidence of nausea was 30% compared with 10% in patients taking a comparable placebo regimen.

In patients taking Varenicline 0.5 mg BID following initial titration, the incidence was 16% compared with 11% for placebo.

Nausea was generally described as mild or moderate and often transient; however, for some subjects, it was persistent throughout the treatment period.

- Table 3 shows the adverse events for Varenicline and placebo in the 12 week fixed dose studies with titration in the first week (Studies 2 (titrated arm only), 4, and 5).

MedDRA High Level Group Terms (HLGT) reported in $\geq 5\%$ of patients in the Varenicline 1 mg BID dose group, and more commonly than in the placebo group, are



listed, along with subordinate Preferred Terms (PT) reported in \geq 1% of Varenicline patients (and at least 0.5% more frequent than placebo).

Closely related Preferred Terms such as 'Insomnia', 'Initial insomnia', 'Middle insomnia', 'Early morning a waking' were grouped, but individual patients reporting two or more grouped events are only counted once.

Table 3: Common Treatment Emergent AEs (%) in the Fixed-Dose, Placebo-Controlled Studies (\geq 1% in the 1 mg BID Varenicline Group, and 1 mg BID Varenicline at least 0.5% more than Placebo)

SYSTEM ORGAN CLASS High Level Group Term Preferred Term	Varenicline 0.5 mg BID N=129	Varenicline 1 mg BID N=821	Placebo N=805
* Includes PTs Abdominal (pain, pain upper, pain lower, discomfort, tenderness, distension) and Stomach discomfort			
**/* Includes PTs Insomnia/Initial insomnia/Middle insomnia/Early morning awakening			
GASTROINTESTINAL			
GI Signs and Symptoms			
Nausea	16	30	10
Abdominal Pain *	5	7	5
Flatulence	9	6	3
Dyspepsia	5	5	3
Vomiting	1	5	2
GI Motility/Defecation Conditions			
Constipation	5	8	3
Gastroesophageal reflux disease	1	1	0
Salivary Gland Conditions			
Dry mouth	4	6	4

Table 3: Common Treatment Emergent AEs (%) in the Fixed-Dose, Placebo-Controlled Studies (>/= 1% in the 1 mg BID Varenicline Group, and 1 mg BID Varenicline at least 0.5% more than Placebo)

SYSTEM ORGAN CLASS High Level Group Term Preferred Term	Varenicline 0.5 mg BID N=129	Varenicline 1 mg BID N=821	Placebo N=805
PSYCHIATRIC DISORDERS			
Sleep Disorder/Disturbances			
Insomnia ^{**/*}	19	18	13
Abnormal dreams	9	13	5
Sleep disorder	2	5	3
Nightmare	2	1	0
NERVOUS SYSTEM			
Headaches			
Headache	19	15	13
Neurological Disorders NEC			
Dysgeusia	8	5	4
Somnolence	3	3	2
Lethargy	2	1	0
GENERAL DISORDERS			
General Disorders NEC			
Fatigue/Malaise/Asthenia	4	7	6
RESPIR/THORACIC/MEDIAST			
Respiratory Disorders NEC			
Rhinorrhea	0	1	0

Table 3: Common Treatment Emergent AEs (%) in the Fixed-Dose, Placebo-Controlled Studies (>/= 1% in the 1 mg BID Varenicline Group, and 1 mg BID Varenicline at least 0.5% more than Placebo)

SYSTEM ORGAN CLASS High Level Group Term Preferred Term	Varenicline 0.5 mg BID N=129	Varenicline 1 mg BID N=821	Placebo N=805
Dyspnoea	2	1	1
Upper Respiratory Tract Disorder	7	5	4
SKIN/SUBCUTANEOUS TISSUE			
Epidermal and Dermal Conditions			
Rash	1	3	2
Pruritus	0	1	1
METABOLISM & NUTRITION			
Appetite/General Nutrit. Disorders			
Increased appetite	4	3	2
Decreased appetite/Anorexia	1	2	1

- The overall pattern, and the frequency of adverse events during the longer-term trials was very similar to that described in Table 3, though several of the most common events were reported by a greater proportion of patients.

Nausea, for instance, was reported in 40% of patients treated with Varenicline 1 mg BID in a one-year study, compared to 8% of placebo-treated patients.

- Following is a list of treatment-emergent adverse events reported by patients treated with Varenicline during all clinical trials.

The listing does not include those events already listed in the previous tables or elsewhere in labeling, those events for which a drug cause was remote, those events

which were so general as to be uninformative, and those events reported only once which did not have a substantial probability of being acutely life-threatening.

BLOOD AND LYMPHATIC SYSTEM DISORDERS.

Infrequent: Anemia, Lymphadenopathy.

Rare: Leukocytosis, Thrombocytopenia, Splenomegaly.

CARDIAC DISORDERS.

Infrequent: Angina pectoris, Arrhythmia, Bradycardia, Ventricular extrasystoles, Myocardial infarction, Palpitations, Tachycardia.

Rare: Atrial fibrillation, Cardiac flutter, Coronary artery disease, Cor pulmonale, Acute coronary syndrome.

EAR AND LABYRINTH DISORDERS.

Infrequent: Tinnitus, Vertigo.

Rare: Deafness, Meniere's disease.

ENDOCRINE DISORDERS.

Infrequent: Thyroid gland disorders.

EYE DISORDERS.

Infrequent: Conjunctivitis, Dry eye, Eye irritation, Vision blurred, Visual disturbance, Eye pain.

Rare: Acquired night blindness, Blindness transient, Cataract subcapsular, Ocular vascular disorder, Photophobia, Vitreous floaters.

GASTROINTESTINAL DISORDERS.

Frequent: Diarrhea, Gingivitis.

Infrequent: Dysphagia, Enterocolitis, Eructation, Gastritis, Gastrointestinal hemorrhage, Mouth ulceration, Esophagitis.

Rare: Gastric ulcer, Intestinal obstruction, Pancreatitis acute.

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS. *Frequent:* Chest pain, Influenza like illness, Edema, Thirst.

Infrequent: Chest discomfort, Chills, Pyrexia.

HEPATOBIILIARY DISORDERS.

Infrequent: Gall bladder disorder.

IMMUNE SYSTEM DISORDERS.

Infrequent: Hypersensitivity.

Rare: Drug hypersensitivity.

INVESTIGATIONS.

Frequent: Liver function test abnormal, Weight increased.

Infrequent: Electrocardiogram abnormal, Muscle enzyme increased, Urine analysis abnormal.

METABOLISM AND NUTRITION DISORDERS.

Infrequent: Diabetes mellitus, Hyperlipidemia, Hypokalemia.

Rare: Hyperkalemia, Hypoglycemia.

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS.

Frequent: Arthralgia, Back pain, Muscle cramp, Musculoskeletal pain, Myalgia.

Infrequent: Arthritis, Osteoporosis.

Rare: Myositis.

NERVOUS SYSTEM DISORDERS.

Frequent: Disturbance in attention, Dizziness, Sensory disturbance.

Infrequent: Amnesia, Migraine, Parosmia, Psychomotor hyperactivity, Restless legs syndrome, Syncope, Tremor.

Rare: Balance disorder, Cerebrovascular accident, Convulsion, Dysarthria, Facial palsy, Mental impairment, Multiple sclerosis, Nystagmus, Psychomotor skills impaired, Transient ischemic attack, Visual field defect.

PSYCHIATRIC DISORDERS.

Frequent: Anxiety, Depression, Emotional disorder, Irritability, Restlessness. **Infrequent:** Aggression, Agitation, Disorientation, Dissociation, Libido decreased, Mood swings, Thinking abnormal.

Rare: Bradyphrenia, Euphoric mood, Hallucination, Psychotic disorder, Suicidal ideation.

RENAL AND URINARY DISORDERS.

Frequent: Polyuria.

Infrequent: Nephrolithiasis, Nocturia, Urine abnormality, Urethral syndrome.

Rare: Renal failure acute, Urinary retention.

REPRODUCTIVE SYSTEM AND BREAST DISORDERS.

Frequent: Menstrual disorder.

Infrequent: Erectile dysfunction.

Rare: Sexual dysfunction.

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS.

Frequent: Epistaxis, Respiratory disorders.

Infrequent: Asthma.

Rare: Pleurisy, Pulmonary embolism.

SKIN AND SUBCUTANEOUS TISSUE DISORDERS.

Frequent: Hyperhidrosis.

Infrequent: Acne, Dermatitis, Dry skin, Eczema, Erythema, Psoriasis, Urticaria.

Rare: Photosensitivity reaction.

VASCULAR DISORDERS.

Frequent: Hot flush, Hypertension.



Infrequent: Hypotension, Peripheral ischemia, Thrombosis.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

Varenicline is not a controlled substance.

Humans:

- Fewer than 1 out of 1000 patients reported euphoria in clinical trials with Varenicline. At higher doses (greater than 2 mg), Varenicline produced more frequent reports of gastrointestinal disturbances such as nausea and vomiting. There is no evidence of dose-escalation to maintain therapeutic effects in clinical studies, which suggests that tolerance does not develop. Abrupt discontinuation of Varenicline was associated with an increase in irritability and sleep disturbances in up to 3% of patients. This suggests that, in some patients, varenicline may produce mild physical dependence which is not associated with addiction.

- In a human laboratory abuse liability study, a single oral dose of 1 mg varenicline did not produce any significant positive or negative subjective responses in smokers. In non-smokers, 1 mg varenicline produced an increase in some positive subjective effects, but this was accompanied by an increase in negative adverse effects, especially nausea. A single oral dose of 3 mg varenicline uniformly produced unpleasant subjective responses in both smokers and non-smokers.

Animals:

Studies in rodents have shown that varenicline produces behavioral responses similar to those produced by nicotine.

In rats trained to discriminate nicotine from saline, varenicline produced full generalization to the nicotine cue.

In self-administration studies, the degree to which varenicline substitutes for nicotine is dependent upon the requirement of the task.





Rats trained to self-administer nicotine under easy conditions continued to self-administer varenicline to a degree comparable to that of nicotine, however in a more demanding task, rats self-administered varenicline to a lesser extent than nicotine. Varenicline pretreatment also reduced nicotine self-administration.

OVERDOSAGE

In case of overdose, standard supportive measures should be instituted as required. Varenicline has been shown to be dialyzed in patients with end stage renal disease, however, there is no experience in dialysis following overdose.

DOSAGE AND ADMINISTRATION

Usual Dosage for Adults

- Smoking cessation therapies are more likely to succeed for patients who are motivated to stop smoking and who are provided additional advice and support. Patients should be provided with appropriate educational materials and counseling to support the quit attempt.
- The patient should set a date to stop smoking. **SmokeLESS** dosing should start one week before this date.
- **SmokeLESS** should be taken after eating and with a full glass of water.
- The recommended dose of **SmokeLESS** 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

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





- Patients should be treated with **SmokeLESS** for 12 weeks. For patients who have successfully stopped smoking at the end of 12 weeks, an additional course of 12 weeks treatment with **SmokeLESS** is recommended to further increase the likelihood of long-term abstinence.

- Patients who do not succeed in stopping smoking during 12 weeks of initial therapy, or who relapse after treatment, should be encouraged to make another attempt once factors contributing to the failed attempt have been identified and addressed.

Special Populations

Patients with impaired renal function

No dosage adjustment is necessary for patients with mild to moderate renal impairment. For patients with severe renal impairment, the recommended starting dose of **SmokeLESS** is 0.5 mg once daily.

Patients may then titrate as needed to a maximum dose of 0.5 mg twice a day.

For patients with end-stage renal disease undergoing hemodialysis, a maximum dose of 0.5 mg once daily may be administered if tolerated well.

Dosing in elderly patients and patients with impaired hepatic function

No dosage adjustment is necessary for patients with hepatic impairment.

Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Use in children

Safety and effectiveness of **SmokeLESS** in pediatric patients have not been established; therefore, **SmokeLESS** is not recommended for use in patients under 18 years of age.

HOW SUPPLIED

- **SmokeLESS** is supplied for oral administration in two strengths: a 0.5 mg capsular biconvex, white to off-white, film-coated tablet, and a 1 mg biconvex, white to off-white, film-coated tablet.

- **SmokeLESS** is supplied in the following package configurations:





SmokeLESS 0.5: Pack contains 11 coated tablets.

SmokeLESS 1: Pack contains 14 coated tablets.

PRODUCT PHOTO(S)

The product samples shown here have been supplied by the manufacturer.



SmokeLESS 0.5 mg



Smokeless[®]
Varenicline 0.5 -1mg



SmokeLESS 0.1 mg

STORAGE AND HANDLING

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

