

CHANTIX- varenicline tartrate tablet, film coated
Aphena Pharma Solutions - Tennessee, LLC

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use CHANTIX safely and effectively. See full prescribing information for CHANTIX.

CHANTIX® (varenicline) tablets, for oral use

Initial U.S. Approval: 2006

----- **RECENT MAJOR CHANGES** -----

Boxed Warning-Removed	12/2016
Dosage and Administration, Usual Dosage for Adults (2.1)	8/2016
Warnings and Precautions, Neuropsychiatric Adverse Events including Suicidality (5.1)	12/2016
Warnings and Precautions, Somnambulism (5.6)	8/2016

----- **INDICATIONS AND USAGE** -----

CHANTIX is a nicotinic receptor partial agonist indicated for use as an aid to smoking cessation treatment. (1 and 2.1)

----- **DOSAGE AND ADMINISTRATION** -----

- Begin CHANTIX dosing one week before the date set by the patient to stop smoking. Alternatively, the patient can begin CHANTIX dosing and then quit smoking between days 8 and 35 of treatment. (2.1)
- Starting week: 0.5 mg once daily on days 1–3 and 0.5 mg twice daily on days 4–7. (2.1)
- Continuing Weeks: 1 mg twice daily for a total of 12 weeks. (2.1)
- An additional 12 weeks of treatment is recommended for successful quitters to increase likelihood of long-term abstinence. (2.1)
- Consider a gradual approach to quitting smoking with CHANTIX for patients who are sure that they are not able or willing to quit abruptly. Patients should begin CHANTIX dosing and 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. Continue treatment for an additional 12 weeks, for a total of 24 weeks. (2.1)
- Severe Renal Impairment (estimated creatinine clearance less than 30 mL/min): Begin with 0.5 mg once daily and titrate to 0.5 mg twice daily. For patients with end-stage renal disease undergoing hemodialysis, a maximum of 0.5 mg daily may be given if tolerated. (2.2)
- Consider dose reduction for patients who cannot tolerate adverse effects. (2.1)
- Another attempt at treatment is recommended for those who fail to stop smoking or relapse when factors contributing to the failed attempt have been addressed. (2.1)
- Provide patients with appropriate educational materials and counseling to support the quit attempt. (2.1)

----- **DOSAGE FORMS AND STRENGTHS** -----

Tablets: 0.5 mg and 1 mg (3)

----- **CONTRAINDICATIONS** -----

History of serious hypersensitivity or skin reactions to CHANTIX. (4)

----- **WARNINGS AND PRECAUTIONS** -----

- Neuropsychiatric Adverse Events: Postmarketing reports of serious or clinically significant neuropsychiatric adverse events have included changes in mood (including depression and mania), psychosis, hallucinations, paranoia, delusions, homicidal ideation, aggression, hostility, agitation, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed suicide. Observe patients attempting to quit smoking with CHANTIX for the occurrence of such symptoms and instruct them to discontinue CHANTIX and contact a healthcare provider if they experience such adverse events. (5.1)
- Seizures: New or worsening seizures have been observed in patients taking CHANTIX. CHANTIX should be used cautiously in patients with a history of seizures or other factors that can lower the seizure threshold. (5.2)
- Interaction with Alcohol: Increased effects of alcohol have been reported. Instruct patients to reduce the amount of alcohol they consume until they know whether CHANTIX affects them. (5.3)
- Accidental Injury: Accidental injuries (e.g., traffic accidents) have been reported. Instruct patients to use caution driving or operating machinery until they know how CHANTIX may affect them. (5.4)
- Cardiovascular Events: A meta-analysis of 15 clinical trials, including a trial in patients with stable cardiovascular (CV) disease, demonstrated that while cardiovascular events were infrequent overall, some were reported more frequently

in patients treated with CHANTIX. These events occurred primarily in patients with known cardiovascular disease. In both the clinical trial and meta-analysis, all-cause and cardiovascular mortality was lower in patients treated with CHANTIX. Instruct patients to notify their healthcare providers of new or worsening cardiovascular symptoms and to seek immediate medical attention if they experience signs and symptoms of myocardial infarction (MI) or stroke. (5.5 and 6.1)

- **Somnambulism:** Cases of somnambulism have been reported in patients taking CHANTIX. Some cases described harmful behavior to self, others, or property. Instruct patients to discontinue CHANTIX and notify their healthcare provider if they experience somnambulism. (5.6 and 6.2)
- **Angioedema and Hypersensitivity Reactions:** Such reactions, including angioedema, infrequently life-threatening, have been reported. Instruct patients to discontinue CHANTIX and immediately seek medical care if symptoms occur. (5.7 and 6.2)
- **Serious Skin Reactions:** Rare, potentially life-threatening skin reactions have been reported. Instruct patients to discontinue CHANTIX and contact a healthcare provider immediately at first appearance of skin rash with mucosal lesions. (5.8 and 6.2)
- **Nausea:** Nausea is the most common adverse reaction (up to 30% incidence rate). Dose reduction may be helpful. (5.9)

----- **ADVERSE REACTIONS** -----

Most common adverse reactions (>5% and twice the rate seen in placebo-treated patients) were nausea, abnormal (e.g., vivid, unusual, or strange) dreams, constipation, flatulence, and vomiting. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer Inc. at 1-800-438-1985 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----- **DRUG INTERACTIONS** -----

- **Other Smoking Cessation Therapies:** Safety and efficacy in combination with other smoking cessation therapies has not been established. Coadministration of varenicline and transdermal nicotine resulted in a high rate of discontinuation due to adverse events. (7.1)
- **Effect of Smoking Cessation on Other Drugs:** Pharmacokinetics or pharmacodynamics of certain drugs (e.g., theophylline, warfarin, insulin) may be altered, necessitating dose adjustment. (7.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2016

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

CHANTIX is indicated for use as an aid to smoking cessation treatment.

2 DOSAGE AND ADMINISTRATION

2.1 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. Provide patients with appropriate educational materials and counseling to support the quit attempt.

The patient should set a date to stop smoking. Begin CHANTIX dosing one week before this date. Alternatively, the patient can begin CHANTIX dosing and then quit smoking between days 8 and 35 of treatment.

CHANTIX should be taken orally after eating and with a full glass of water.

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

For patients who are sure that they are not able or willing to quit abruptly, consider a gradual approach to quitting smoking with CHANTIX. Patients should begin CHANTIX dosing and 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. Continue CHANTIX treatment for an additional 12 weeks, for a total of 24 weeks of treatment. Encourage patients to attempt quitting sooner if they feel ready [see *Clinical Studies (14.5)*].

Patients who are motivated to quit, and who did not succeed in stopping smoking during prior CHANTIX therapy for reasons other than intolerability due to adverse events or who relapsed after treatment, should be encouraged to make another attempt with CHANTIX once factors contributing to the failed attempt have been identified and addressed.

Consider a temporary or permanent dose reduction in patients who cannot tolerate the adverse effects of CHANTIX.

2.2 Dosage in 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 (estimated creatinine clearance less than 30 mL per min), the recommended starting dose of CHANTIX is 0.5 mg once daily. The dose may then be titrated as needed to a maximum dose of 0.5 mg twice daily. For patients with end-stage renal disease undergoing hemodialysis, a maximum dose of 0.5 mg once daily may be administered if tolerated [see *Use in Specific Populations (8.6)*, *Clinical Pharmacology (12.3)*].

Elderly 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 [see *Use in Specific Populations (8.5)*].

3 DOSAGE FORMS AND STRENGTHS

Capsular, biconvex tablets: 0.5 mg (white to off-white, debossed with "Pfizer" on one side and "CHX 0.5" on the other side) and 1 mg (light blue, debossed with "Pfizer" on one side and "CHX 1.0" on the other side).

4 CONTRAINDICATIONS

CHANTIX is contraindicated in patients with a known history of serious hypersensitivity reactions or skin reactions to CHANTIX.

5 WARNINGS AND PRECAUTIONS

5.1 Neuropsychiatric Adverse Events including Suicidality

Serious neuropsychiatric adverse events have been reported in patients being treated with CHANTIX

[see *Adverse Reactions (6.2)*]. These postmarketing reports have included changes in mood (including depression and mania), psychosis, hallucinations, paranoia, delusions, homicidal ideation, aggression, hostility, agitation, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed suicide. Some patients who stopped smoking may have been experiencing symptoms of nicotine withdrawal, including depressed mood. Depression, rarely including suicidal ideation, has been reported in smokers undergoing a smoking cessation attempt without medication. However, some of these adverse events occurred in patients taking CHANTIX who continued to smoke.

Neuropsychiatric adverse events occurred in patients without and with pre-existing psychiatric disease; some patients experienced worsening of their psychiatric illnesses. Some neuropsychiatric adverse events, including unusual and sometimes aggressive behavior directed to oneself or others, may have been worsened by concomitant use of alcohol [see *Warnings and Precautions (5.3)*, *Adverse Reactions (6.2)*]. Observe patients for the occurrence of neuropsychiatric adverse events. Advise patients and caregivers that the patient should stop taking CHANTIX and contact a healthcare provider immediately if agitation, depressed mood, or changes in behavior or thinking that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behavior. The healthcare provider should evaluate the severity of the symptoms and the extent to which the patient is benefiting from treatment, and consider options including dose reduction, continued treatment under closer monitoring, or discontinuing treatment. In many postmarketing cases, resolution of symptoms after discontinuation of CHANTIX was reported. However, the symptoms persisted in some cases; therefore, ongoing monitoring and supportive care should be provided until symptoms resolve.

The neuropsychiatric safety of CHANTIX was evaluated in a randomized, double-blind, active and placebo-controlled study that included patients without a history of psychiatric disorder (non-psychiatric cohort, N=3912) and patients with a history of psychiatric disorder (psychiatric cohort, N=4003). In the non-psychiatric cohort, CHANTIX was not associated with an increased incidence of clinically significant neuropsychiatric adverse events in a composite endpoint comprising anxiety, depression, feeling abnormal, hostility, agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, and irritability. In the psychiatric cohort, there were more events reported in each treatment group compared to the non-psychiatric cohort, and the incidence of events in the composite endpoint was higher for each of the active treatments compared to placebo: Risk Differences (RDs) (95%CI) vs. placebo were 2.7% (-0.05, 5.4) for CHANTIX, 2.2% (-0.5, 4.9) for bupropion, and 0.4% (-2.2, 3.0) for transdermal nicotine. In the non-psychiatric cohort, neuropsychiatric adverse events of a serious nature were reported in 0.1% of CHANTIX-treated patients and 0.4% of placebo-treated patients. In the psychiatric cohort, neuropsychiatric events of a serious nature were reported in 0.6% of CHANTIX-treated patients, with 0.5% involving psychiatric hospitalization. In placebo-treated patients, serious neuropsychiatric events occurred in 0.6%, with 0.2% requiring psychiatric hospitalization [see *Clinical Studies (14.9)*].

5.2 Seizures

During clinical trials and the post marketing experience, there have been reports of seizures in patients treated with CHANTIX. Some patients had no history of seizures, whereas others had a history of seizure disorder that was remote or well-controlled. In most cases, the seizure occurred within the first month of therapy. Weigh this potential risk against the potential benefits before prescribing CHANTIX in patients with a history of seizures or other factors that can lower the seizure threshold. Advise patients to discontinue CHANTIX and contact a healthcare provider immediately if they experience a seizure while on treatment [see *Adverse Reactions (6.2)*].

5.3 Interaction with Alcohol

There have been postmarketing reports of patients experiencing increased intoxicating effects of alcohol while taking CHANTIX. Some cases described unusual and sometimes aggressive behavior, and were often accompanied by amnesia for the events. Advise patients to reduce the amount of alcohol they consume while taking CHANTIX until they know whether CHANTIX affects their tolerance for

alcohol [see Adverse Reactions (6.2)].

5.4 Accidental Injury

There have been postmarketing reports of traffic accidents, near-miss incidents in traffic, or other accidental injuries in patients taking CHANTIX. In some cases, the patients reported somnolence, dizziness, loss of consciousness or difficulty concentrating that resulted in impairment, or concern about potential impairment, in driving or operating machinery. Advise patients to use caution driving or operating machinery or engaging in other potentially hazardous activities until they know how CHANTIX may affect them.

5.5 Cardiovascular Events

In a placebo-controlled clinical trial of CHANTIX administered to patients with stable cardiovascular disease, with approximately 350 patients per treatment arm, all-cause and cardiovascular mortality was lower in patients treated with CHANTIX, but certain nonfatal cardiovascular events occurred more frequently in patients treated with CHANTIX than in patients treated with placebo [see Adverse Reactions (6.1)]. Table 1 below shows the incidence of deaths and of selected nonfatal serious cardiovascular events occurring more frequently in the CHANTIX arm compared to the placebo arm. These events were adjudicated by an independent blinded committee. Nonfatal serious cardiovascular events not listed occurred at the same incidence or more commonly in the placebo arm. Patients with more than one cardiovascular event of the same type are counted only once per row. Some of the patients requiring coronary revascularization underwent the procedure as part of management of nonfatal MI and hospitalization for angina.

Table 1. Mortality and Adjudicated Nonfatal Serious Cardiovascular Events in the Placebo-Controlled CHANTIX Trial in Patients with Stable Cardiovascular Disease

Mortality and Cardiovascular Events	CHANTIX (N=353) n (%)	Placebo (N=350) n (%)
<i>Mortality (Cardiovascular & All-cause up to 52 wks)</i>		
Cardiovascular death	1 (0.3)	2 (0.6)
All-cause mortality	2 (0.6)	5 (1.4)
<i>Nonfatal Cardiovascular Events (rate on CHANTIX > Placebo)</i>		
<i>Up to 30 days after treatment</i>		
Nonfatal myocardial infarction	4 (1.1)	1 (0.3)
Nonfatal Stroke	2 (0.6)	0 (0)
<i>Beyond 30 days after treatment & up to 52 weeks</i>		
Nonfatal myocardial infarction	3 (0.8)	2 (0.6)
Need for coronary revascularization	7 (2.0)	2 (0.6)
Hospitalization for angina pectoris	6 (1.7)	4 (1.1)
Transient ischemia attack	1 (0.3)	0 (0)
New diagnosis of peripheral vascular disease (PVD) or admission for a PVD procedure	5 (1.4)	2 (0.6)

A meta-analysis of 15 clinical trials of ≥ 12 weeks treatment duration, including 7002 patients (4190 CHANTIX, 2812 placebo), was conducted to systematically assess the cardiovascular safety of CHANTIX. The study in patients with stable cardiovascular disease described above was included in the meta-analysis. There were lower rates of all-cause mortality (CHANTIX 6 [0.14%]; placebo 7 [0.25%]) and cardiovascular mortality (CHANTIX 2 [0.05%]; placebo 2 [0.07%]) in the CHANTIX arms compared with the placebo arms in the meta-analysis.

The key cardiovascular safety analysis included occurrence and timing of a composite endpoint of Major Adverse Cardiovascular Events (MACE), defined as cardiovascular death, nonfatal MI, and nonfatal stroke. These events included in the endpoint were adjudicated by a blinded, independent committee. Overall, a small number of MACE occurred in the trials included in the meta-analysis, as described in Table 2. These events occurred primarily in patients with known cardiovascular disease.

Table 2. Number of MACE cases, Hazard Ratio and Rate Difference in a Meta-Analysis of 15 Clinical Trials Comparing CHANTIX to Placebo*

	CHANTIX N=4190	Placebo N=2812
MACE cases, n (%)	13 (0.31%)	6 (0.21%)
Patient-years of exposure	1316	839
Hazard Ratio (95% CI)		
	1.95 (0.79, 4.82)	
Rate Difference per 1,000 patient-years (95% CI)		
	6.30 (-2.40, 15.10)	

* Includes MACE occurring up to 30 days post-treatment.

The meta-analysis showed that exposure to CHANTIX resulted in a hazard ratio for MACE of 1.95 (95% confidence interval from 0.79 to 4.82) for patients up to 30 days after treatment; this is equivalent to an estimated increase of 6.3 MACE events per 1,000 patient-years of exposure. The meta-analysis showed higher rates of CV endpoints in patients on CHANTIX relative to placebo across different time frames and pre-specified sensitivity analyses, including various study groupings and CV outcomes. Although these findings were not statistically significant they were consistent. Because the number of events was small overall, the power for finding a statistically significant difference in a signal of this magnitude is low.

CHANTIX was not studied in patients with unstable cardiovascular disease or cardiovascular events occurring within two months before screening. Patients should be advised to notify a healthcare provider of new or worsening symptoms of cardiovascular disease. The risks of CHANTIX should be weighed against the benefits of its use in smokers with cardiovascular disease. Smoking is an independent and major risk factor for cardiovascular disease. CHANTIX has been demonstrated to increase the likelihood of abstinence from smoking for as long as one year compared to treatment with placebo.

5.6 Somnambulism

Cases of somnambulism have been reported in patients taking CHANTIX. Some cases described harmful behavior to self, others, or property. Instruct patients to discontinue CHANTIX and notify their healthcare provider if they experience somnambulism [see *Adverse Reactions (6.2)*].

5.7 Angioedema and Hypersensitivity Reactions

There have been postmarketing reports of hypersensitivity reactions including angioedema in patients treated with CHANTIX [see *Adverse Reactions (6.2)*, *Patient Counseling Information (17)*]. Clinical signs included swelling of the face, mouth (tongue, lips, and gums), extremities, and neck (throat and larynx). There were infrequent reports of life-threatening angioedema requiring emergent medical attention due to respiratory compromise. Instruct patients to discontinue CHANTIX and immediately seek medical care if they experience these symptoms.

5.8 Serious Skin Reactions

There have been postmarketing reports of rare but serious skin reactions, including Stevens-Johnson

Syndrome and erythema multiforme, in patients using CHANTIX [see *Adverse Reactions (6.2)*]. As these skin reactions can be life-threatening, instruct patients to stop taking CHANTIX and contact a healthcare provider immediately at the first appearance of a skin rash with mucosal lesions or any other signs of hypersensitivity.

5.9 Nausea

Nausea was the most common adverse reaction reported with CHANTIX treatment. Nausea was generally described as mild or moderate and often transient; however, for some patients, it was persistent over several months. The incidence of nausea was dose-dependent. Initial dose-titration was beneficial in reducing the occurrence of nausea. For patients treated to the maximum recommended dose of 1 mg twice daily following initial dosage titration, the incidence of nausea was 30% compared with 10% in patients taking a comparable placebo regimen. In patients taking CHANTIX 0.5 mg twice daily following initial titration, the incidence was 16% compared with 11% for placebo. Approximately 3% of patients treated with CHANTIX 1 mg twice daily in studies involving 12 weeks of treatment discontinued treatment prematurely because of nausea. For patients with intolerable nausea, a dose reduction should be considered.

6 ADVERSE REACTIONS

The following serious adverse reactions were reported in postmarketing experience and are discussed in greater detail in other sections of the labeling:

- Neuropsychiatric Adverse Events including Suicidality [see *Warnings and Precautions (5.1)*]
- Seizures [see *Warnings and Precautions (5.2)*]
- Interaction with alcohol [see *Warnings and Precautions (5.3)*]
- Accidental injury [see *Warnings and Precautions (5.4)*]
- Cardiovascular events [see *Warnings and Precautions (5.5)*]
- Somnambulism [see *Warnings and Precautions (5.6)*]
- Angioedema and hypersensitivity reactions [see *Warnings and Precautions (5.7)*]
- Serious skin reactions [see *Warnings and Precautions (5.8)*]

In the placebo-controlled premarketing studies, the most common adverse events associated with CHANTIX (>5% and twice the rate seen in placebo-treated patients) were nausea, abnormal (vivid, unusual, or strange) dreams, constipation, flatulence, and vomiting.

The treatment discontinuation rate due to adverse events in patients dosed with 1 mg twice daily was 12% for CHANTIX, compared to 10% for placebo in studies of three months' treatment. In this group, the discontinuation rates that are higher than placebo for the most common adverse events in CHANTIX-treated patients were as follows: nausea (3% vs. 0.5% for placebo), insomnia (1.2% vs. 1.1% for placebo), and abnormal dreams (0.3% vs. 0.2% for placebo).

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

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the adverse reactions rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

During the premarketing development of CHANTIX, over 4500 subjects were exposed to CHANTIX, 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.

The most common adverse event associated with CHANTIX treatment is nausea, occurring in 30% of patients treated at the recommended dose, compared with 10% in patients taking a comparable placebo

regimen [see Warnings and Precautions (5.9)].

Table 3 shows the adverse events for CHANTIX and placebo in the 12- week fixed dose premarketing studies with titration in the first week [Studies 2 (titrated arm only), 4, and 5]. Adverse events were categorized using the Medical Dictionary for Regulatory Activities (MedDRA, Version 7.1).

MedDRA High Level Group Terms (HLGT) reported in $\geq 5\%$ of patients in the CHANTIX 1 mg twice daily dose group, and more commonly than in the placebo group, are listed, along with subordinate Preferred Terms (PT) reported in $\geq 1\%$ of CHANTIX patients (and at least 0.5% more frequent than placebo). Closely related Preferred Terms such as 'Insomnia', 'Initial insomnia', 'Middle insomnia', 'Early morning awakening' 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 (HLGTs $\geq 5\%$ of patients in the 1 mg BID CHANTIX Group and more commonly than Placebo and PT $\geq 1\%$ in the 1 mg BID CHANTIX Group, and 1 mg BID CHANTIX at least 0.5% more than Placebo)

SYSTEM ORGAN CLASS High Level Group Term Preferred Term	CHANTIX 0.5 mg BID N=129	CHANTIX 1 mg BID N=821	Placebo N=805
GASTROINTESTINAL (GI)			
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
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
Dyspnea	2	1	1
Upper Respiratory Tract Disorder	7	5	4
SKIN/SUBCUTANEOUS TISSUE			
Epidermal and Dermal Conditions			
Rash	1	3	2
Pruritis	0	1	1
METABOLISM & NUTRITION			
Appetite/General Nutrition Disorders			
Increased appetite	4	3	2
Decreased appetite/Anorexia	1	2	1

* Includes PTs Abdominal (pain, pain upper, pain lower, discomfort, tenderness, distension) and Stomach discomfort

† Includes PTs Insomnia/Initial insomnia/Middle insomnia/Early morning awakening

The overall pattern and frequency of adverse events during the longer-term premarketing trials was similar to those described in Table 3, though several of the most common events were reported by a greater proportion of patients with long-term use (e.g., nausea was reported in 40% of patients treated with CHANTIX 1 mg twice daily 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 CHANTIX during all premarketing clinical trials and updated based on pooled data from 18 placebo-controlled pre- and post-marketing studies, including approximately 5,000 patients treated with varenicline. Adverse events were categorized using MedDRA, Version 16.0. 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, splenomegaly, thrombocytopenia.

Cardiac Disorders. *Infrequent:* angina pectoris, myocardial infarction, palpitations, tachycardia. *Rare:* acute coronary syndrome, arrhythmia, atrial fibrillation, bradycardia, cardiac flutter, cor pulmonale, coronary artery disease, ventricular extrasystoles.

Ear and Labyrinth Disorders. *Infrequent:* tinnitus, vertigo. *Rare:* deafness, Meniere's disease.

Endocrine Disorders. *Infrequent:* thyroid gland disorders.

Eye Disorders. *Infrequent:* conjunctivitis, eye irritation, eye pain, vision blurred, visual impairment. *Rare:* blindness transient, cataract subcapsular, dry eye, night blindness, ocular vascular disorder, photophobia, vitreous floaters.

Gastrointestinal Disorders. *Frequent:* diarrhea, toothache. *Infrequent:* dysphagia, eructation, gastritis, gastrointestinal hemorrhage, mouth ulceration. *Rare:* enterocolitis, esophagitis, gastric ulcer, intestinal obstruction, pancreatitis acute.

General Disorders and Administration Site Conditions. *Frequent:* chest pain. *Infrequent:* chest discomfort, chills, edema, influenza-like illness, pyrexia.

Hepatobiliary Disorders. *Rare:* gall bladder disorder.

Investigations. *Frequent:* liver function test abnormal, weight increased. *Infrequent:* electrocardiogram abnormal. *Rare:* muscle enzyme increased, urine analysis abnormal.

Metabolism and Nutrition Disorders. *Infrequent:* diabetes mellitus, hypoglycemia. *Rare:* hyperlipidemia,

hypokalemia.

Musculoskeletal and Connective Tissue Disorders. *Frequent:* arthralgia, back pain, myalgia. *Infrequent:* arthritis, muscle cramp, musculoskeletal pain. *Rare:* myositis, osteoporosis.

Nervous System Disorders. *Frequent:* disturbance in attention, dizziness. *Infrequent:* amnesia, convulsion, migraine, parosmia, syncope, tremor. *Rare:* balance disorder, cerebrovascular accident, dysarthria, mental impairment, multiple sclerosis, VIIth nerve paralysis, nystagmus, psychomotor hyperactivity, psychomotor skills impaired, restless legs syndrome, sensory disturbance, transient ischemic attack, visual field defect.

Psychiatric Disorders. *Infrequent:* dissociation, libido decreased, mood swings, thinking abnormal. *Rare:* bradyphrenia, disorientation, euphoric mood.

Renal and Urinary Disorders. *Infrequent:* nocturia, pollakiuria, urine abnormality. *Rare:* nephrolithiasis, polyuria, renal failure acute, urethral syndrome, urinary retention.

Reproductive System and Breast Disorders. *Frequent:* menstrual disorder. *Infrequent:* erectile dysfunction. *Rare:* sexual dysfunction.

Respiratory, Thoracic and Mediastinal Disorders. *Frequent:* respiratory disorders. *Infrequent:* asthma, epistaxis, rhinitis allergic, upper respiratory tract inflammation. *Rare:* pleurisy, pulmonary embolism.

Skin and Subcutaneous Tissue Disorders. *Infrequent:* acne, dry skin, eczema, erythema, hyperhidrosis, urticaria. *Rare:* photosensitivity reaction, psoriasis.

Vascular Disorders. *Infrequent:* hot flush. *Rare:* thrombosis.

CHANTIX has also been studied in postmarketing trials including (1) a trial conducted in patients with chronic obstructive pulmonary disease (COPD), (2) a trial conducted in generally healthy patients (similar to those in the premarketing studies) in which they were allowed to select a quit date between days 8 and 35 of treatment ("alternative quit date instruction trial"), (3) a trial conducted in patients who did not succeed in stopping smoking during prior CHANTIX therapy, or who relapsed after treatment ("re-treatment trial"), (4) a trial conducted in patients with stable cardiovascular disease, (5) a trial conducted in patients with stable schizophrenia or schizoaffective disorder, (6) a trial conducted in patients with major depressive disorder, (7) a postmarketing neuropsychiatric safety outcome trial in patients without or with a history of psychiatric disorder, and (8) a trial in patients who were not able or willing to quit abruptly and who were instructed to quit gradually ("gradual approach to quitting smoking trial").

Adverse events in the trial of patients with COPD, in the alternative quit date instruction trial, and in the gradual approach to quitting smoking trial were similar to those observed in premarketing studies. In the re-treatment trial, the profile of common adverse events was similar to that previously reported, but, in addition, varenicline-treated patients also commonly reported diarrhea (6% vs. 4% in placebo-treated patients), depressed mood disorders and disturbances (6% vs. 1%), and other mood disorders and disturbances (5% vs. 2%).

In the trial of patients with stable cardiovascular disease, more types and a greater number of cardiovascular events were reported compared to premarketing studies. Treatment-emergent (on-treatment or 30 days after treatment) cardiovascular events reported with a frequency $\geq 1\%$ in either treatment group in this study were angina pectoris (3.7% and 2.0% for varenicline and placebo, respectively), chest pain (2.5% vs. 2.3%), peripheral edema (2.0% vs. 1.1%), hypertension (1.4% vs. 2.6%), and palpitations (0.6% vs. 1.1%). Deaths and serious cardiovascular events occurring over the 52 weeks of the study (treatment emergent and non-treatment emergent) were adjudicated by a blinded, independent committee. The following treatment-emergent adjudicated events occurred with a frequency $\geq 1\%$ in either treatment group: nonfatal MI (1.1% vs. 0.3% for varenicline and placebo, respectively), and hospitalization for angina pectoris (0.6% vs. 1.1%). During non-treatment follow-up to 52 weeks, the adjudicated events included need for coronary revascularization (2.0% vs. 0.6%), hospitalization for angina pectoris (1.7% vs. 1.1%), and new diagnosis of peripheral vascular disease (PVD) or admission

for a PVD procedure (1.4% vs. 0.6%). Some of the patients requiring coronary revascularization underwent the procedure as part of management of nonfatal MI and hospitalization for angina. Cardiovascular death occurred in 0.3% of patients in the varenicline arm and 0.6% of patients in the placebo arm over the course of the 52-week study.

In the trial of patients with stable schizophrenia or schizoaffective disorder, 128 smokers on antipsychotic medication were randomized 2:1 to varenicline (1 mg twice daily) or placebo for 12 weeks with 12-week non-drug follow-up. The most common adverse events in patients taking varenicline were nausea (24% vs. 14.0% on placebo), headache (11% vs. 19% on placebo) and vomiting (11% vs. 9% on placebo). Among reported neuropsychiatric adverse events, insomnia was the only event that occurred in either treatment group in $\geq 5\%$ of subjects at a rate higher in the varenicline group than in placebo (10% vs. 5%). These common and neuropsychiatric adverse events occurred on treatment or within 30 days after the last dose of study drug. There was no consistent worsening of schizophrenia in either treatment group as measured by the Positive and Negative Syndrome Scale. There were no overall changes in extra-pyramidal signs, as measured by the Simpson-Angus Rating Scale. The Columbia-Suicide Severity Rating Scale was administered at baseline and at clinic visits during the treatment and non-treatment follow-up phases. Over half of the patients had a lifetime history of suicidal behavior and/or ideation (62% on varenicline vs. 51% on placebo), but at baseline, no patients in the varenicline group reported suicidal behavior and/or ideation vs. one patient in the placebo group (2%). Suicidal behavior and/or ideation were reported in 11% of the varenicline-treated and 9% of the placebo-treated patients during the treatment phase. During the post-treatment phase, suicidal behavior and/or ideation were reported in 11% of patients in the varenicline group and 5% of patients in the placebo group. Many of the patients reporting suicidal behavior and ideation in the follow-up phase had not reported such experiences in the treatment phase. However, no new suicidal ideation or behavior emerged in either treatment group shortly (within one week) after treatment discontinuation (a phenomenon noted in postmarketing reporting). There were no completed suicides. There was one suicide attempt in a varenicline-treated patient. The limited data available from this single smoking cessation study are not sufficient to allow conclusions to be drawn.

In the trial of patients with major depressive disorder, the most common adverse events ($\geq 10\%$) in subjects taking varenicline were nausea (27% vs. 10% on placebo), headache (17 vs. 11%), abnormal dreams (11% vs. 8%), insomnia (11% vs. 5%) and irritability (11% vs. 8%). Additionally, the following psychiatric AEs were reported in $\geq 2\%$ of patients in either treatment group (varenicline or placebo, respectively): anxiety (7% vs. 9%), agitation (7% vs. 4%), depressed mood disorders and disturbances (11% vs. 9%), tension (4% vs. 3%), hostility (2% vs. 0.4%) and restlessness (2% vs. 2%). Patients treated with varenicline were more likely than patients treated with placebo to report one of various events related to hostility and aggression (3% vs. 1%). 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 behavior was similar between the varenicline and placebo groups during treatment (6% and 8%, respectively) and the non-treatment follow-up (6% and 6%, respectively). There was one event of intentional self-injury/possible suicide attempt during treatment (Day 73) in a subject in the placebo group. Suicide could not be ruled out in one subject who died by an overdose of illicit drugs 76 days after last dose of study drug in the varenicline group.

In the trial of patients without or with a history of psychiatric disorder, the most common adverse events in subjects treated with varenicline were similar to those observed in premarketing studies. Adverse events reported in $\geq 10\%$ of subjects treated with varenicline in the entire study population were nausea (25% vs. 7% on placebo) and headache (12% vs. 10% on placebo). Additionally, the following psychiatric adverse events were reported in $\geq 2\%$ of patients in either treatment group (varenicline vs. placebo) by cohort. For the non-psychiatric cohort, these adverse events were abnormal dreams (8% vs. 4%), agitation (3% vs. 3%), anxiety (5% vs. 6%), depressed mood (3% vs. 3%), insomnia (10% vs. 7%), irritability (3% vs. 4%), sleep disorder (3% vs. 2%). For the psychiatric cohort, these adverse events were abnormal dreams (12% vs. 5%), agitation (5% vs. 4%), anxiety (8% vs. 6%), depressed mood (5%

vs. 5%), depression (5% vs. 5%), insomnia (9% vs. 7%), irritability (5% vs. 7%), nervousness (2% vs. 3%), sleep disorder (3% vs. 2%).

6.2 Postmarketing Experience

The following adverse events have been reported during post-approval use of CHANTIX. Because these events are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

There have been reports of depression, mania, psychosis, hallucinations, paranoia, delusions, homicidal ideation, aggression, hostility, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed suicide in patients attempting to quit smoking while taking CHANTIX [see *Warnings and Precautions (5.1)*].

There have been postmarketing reports of new or worsening seizures in patients treated with CHANTIX [see *Warnings and Precautions (5.2)*].

There have been postmarketing reports of patients experiencing increased intoxicating effects of alcohol while taking CHANTIX. Some reported neuropsychiatric events, including unusual and sometimes aggressive behavior [see *Warnings and Precautions (5.1) and (5.3)*].

There have been reports of hypersensitivity reactions, including angioedema [see *Warnings and Precautions (5.7)*].

There have also been reports of serious skin reactions, including Stevens-Johnson Syndrome and erythema multiforme, in patients taking CHANTIX [see *Warnings and Precautions (5.8)*].

There have been reports of myocardial infarction (MI) and cerebrovascular accident (CVA) including ischemic and hemorrhagic events in patients taking CHANTIX. 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 [see *Warnings and Precautions (5.5)*].

There have been reports of hyperglycemia in patients following initiation of CHANTIX.

There have been reports of somnambulism, some resulting in harmful behavior to self, others, or property in patients treated with CHANTIX [see *Warnings and Precautions (5.6)*].

7 DRUG INTERACTIONS

Based on varenicline characteristics and clinical experience to date, CHANTIX has no clinically meaningful pharmacokinetic drug interactions [see *Clinical Pharmacology (12.3)*].

7.1 Use with Other Drugs for Smoking Cessation

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

Bupropion

Varenicline (1 mg twice daily) did not alter the steady-state pharmacokinetics of bupropion (150 mg twice daily) 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 twice daily) 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%) patients treated with the combination of varenicline and NRT prematurely discontinued treatment due to adverse events, compared to 1 of 17 (6%) of patients treated with NRT and

placebo.

7.2 Effect of Smoking Cessation on Other Drugs

Physiological changes resulting from smoking cessation, with or without treatment with CHANTIX, may alter the pharmacokinetics or pharmacodynamics of certain drugs (e.g., theophylline, warfarin, insulin) for which dosage adjustment may be necessary.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available human data on the use of CHANTIX in pregnant women are not sufficient to inform a drug associated risk. Smoking during pregnancy is associated with maternal, fetal, and neonatal risks [see *Clinical Considerations*]. In animal studies, varenicline did not result in major malformations but caused decreased fetal weights in rabbits when dosed during organogenesis at exposures equivalent to 50 times the exposure at the maximum recommended human dose (MRHD). Additionally, administration of varenicline to pregnant rats during organogenesis through lactation produced developmental toxicity in offspring at maternal exposures equivalent to 36 times human exposure at the MRHD [see *Data*].

The estimated background risk of oral clefts is increased by approximately 30% in infants of women who smoke during pregnancy, compared to pregnant women who do not smoke. The background risk of other major birth defects and miscarriage for the indicated population are unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2–4% and 15–20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Smoking during pregnancy causes increased risks of orofacial clefts, premature rupture of membranes, placenta previa, placental abruption, ectopic pregnancy, fetal growth restriction and low birth weight, stillbirth, preterm delivery and shortened gestation, neonatal death, sudden infant death syndrome and reduction of lung function in infants. It is not known whether quitting smoking with CHANTIX during pregnancy reduces these risks.

Data

Animal Data

Pregnant rats and rabbits received varenicline succinate during organogenesis at oral doses up to 15 and 30 mg/kg/day, respectively. While no fetal structural abnormalities occurred in either species, maternal toxicity, characterized by reduced body weight gain, and reduced fetal weights occurred in rabbits at the highest dose (exposures 50 times the human exposure at the MRHD of 1 mg twice daily based on AUC). Fetal weight reduction did not occur in rabbits at exposures 23 times the human exposure at the MRHD based on AUC.

In a pre- and postnatal development study, pregnant rats received up to 15 mg/kg/day of oral varenicline succinate from organogenesis through lactation. Maternal toxicity, characterized by a decrease in body weight gain was observed at 15 mg/kg/day (36 times the human exposure at the MRHD based on AUC). However, decreased fertility and increased auditory startle response occurred in offspring at the highest maternal dose of 15 mg/kg/day.

8.2 Lactation

Risk Summary

There are no data on the presence of varenicline in human milk, the effects on the breastfed infant, or the

effects on milk production. In animal studies varenicline was present in milk of lactating rats [see Data]. However, due to species-specific differences in lactation physiology, animal data may not reliably predict drug levels in human milk. The lack of clinical data during lactation precludes a clear determination of the risk of CHANTIX to an infant during lactation; however the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for CHANTIX and any potential adverse effects on the breastfed child from CHANTIX or from the underlying maternal condition.

Clinical Considerations

Because there are no data on the presence of varenicline in human milk and the effects on the breastfed infant, breastfeeding women should monitor their infant for seizures and excessive vomiting, which are adverse reactions that have occurred in adults that may be clinically relevant in breastfeeding infants.

Data

In a pre- and postnatal development study, pregnant rats received up to 15 mg/kg/day of oral varenicline succinate through gestation and lactation. Mean serum concentrations of varenicline in the nursing pups were 5–22% of maternal serum concentrations.

8.4 Pediatric Use

Safety and effectiveness of CHANTIX in pediatric patients have not been established.

8.5 Geriatric Use

A combined single- and multiple-dose pharmacokinetic study demonstrated that the pharmacokinetics of 1 mg varenicline given once daily or twice daily to 16 healthy elderly male and female smokers (aged 65–75 years) for 7 consecutive days was similar to that of younger subjects. 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 [see *Dosage and Administration (2.2)*].

No dosage adjustment is recommended for elderly patients.

8.6 Renal Impairment

Varenicline is substantially eliminated by renal glomerular filtration along with active tubular secretion. Dose reduction is not required in patients with mild to moderate renal impairment. For patients with severe renal impairment (estimated creatinine clearance <30 mL/min), and for patients with end-stage renal disease undergoing hemodialysis, dosage adjustment is needed [see *Dosage and Administration (2.2)*, *Clinical Pharmacology (12.3)*].

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Varenicline is not a controlled substance.

9.3 Dependence

Humans

Fewer than 1 out of 1,000 patients reported euphoria in clinical trials with CHANTIX. At higher doses (greater than 2 mg), CHANTIX 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 CHANTIX 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.

10 OVERDOSAGE

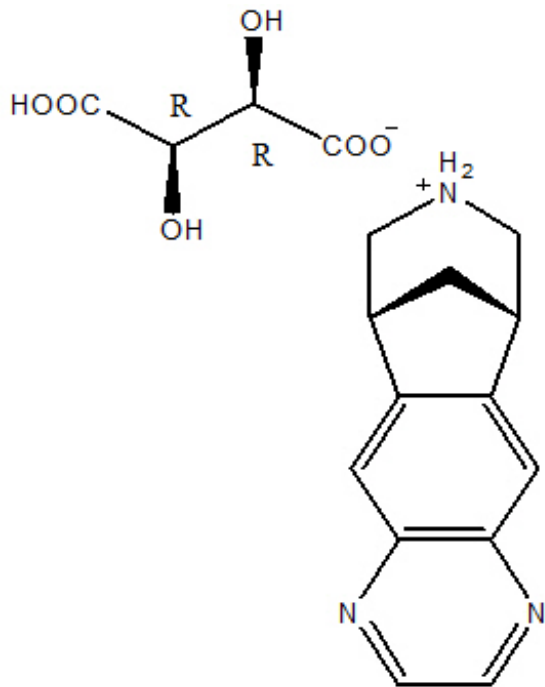
In case of overdose, standard supportive measures should be instituted as required.

Varenicline has been shown to be dialyzed in patients with end-stage renal disease [see *Clinical Pharmacology* (12.3)], however, there is no experience in dialysis following overdose.

11 DESCRIPTION

CHANTIX tablets contain varenicline (as the tartrate salt), which is a partial nicotinic 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, (2R,3R)-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 $C_{13}H_{13}N_3 \cdot C_4H_6O_6$. The chemical structure is:



CHANTIX is supplied for oral administration in two strengths: a 0.5 mg capsular biconvex, white to off-white, film-coated tablet debossed with "Pfizer" on one side and "CHX 0.5" on the other side and a 1 mg capsular biconvex, light blue film-coated tablet debossed with "Pfizer" on one side and "CHX 1.0" on the other side. Each 0.5 mg CHANTIX tablet contains 0.85 mg of varenicline tartrate equivalent to 0.5 mg of varenicline free base; each 1 mg CHANTIX tablet contains 1.71 mg of varenicline tartrate equivalent to 1 mg of varenicline free base. The following inactive ingredients are included in the tablets: microcrystalline cellulose, anhydrous dibasic calcium phosphate, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, Opadry® White (for 0.5 mg), Opadry® Blue (for 1 mg), and Opadry® Clear.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Varenicline binds with high affinity and selectivity at $\alpha 4\beta 2$ neuronal nicotinic acetylcholine receptors. The efficacy of CHANTIX in smoking cessation is believed to be the result of varenicline's activity at $\alpha 4\beta 2$ sub-type of the nicotinic receptor where its binding produces agonist activity, while simultaneously preventing nicotine binding to these 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 $\alpha 3\beta 4$, >3,500-fold $\alpha 7$, >20,000-fold $\alpha 1\beta \gamma \delta$), or to non-nicotinic receptors and transporters (>2,000-fold). Varenicline also binds with moderate affinity ($K_i = 350$ nM) to the 5-HT₃ receptor.

12.3 Pharmacokinetics

Absorption

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 ~90%.

Food Effect

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

Distribution

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

Elimination

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

Metabolism

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

Excretion

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

Specific 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.

Age: Geriatric Patients

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

Age: Pediatric Patients

Because the safety and effectiveness of CHANTIX in pediatric patients have not been established, CHANTIX is not recommended for use in patients under 18 years of age. Single and multiple-dose pharmacokinetics of varenicline have been investigated in pediatric patients aged 12 to 17 years old (inclusive) and were approximately dose-proportional over the 0.5 mg to 2 mg daily dose range studied. Steady-state systemic exposure in adolescent patients of bodyweight > 55 kg, as assessed by AUC (0–24), was comparable to that noted for the same doses in the adult population. When 0.5 mg BID was given, steady-state daily exposure of varenicline was, on average, higher (by approximately 40%) in adolescent patients with bodyweight ≤ 55 kg compared to that noted in the adult population.

Renal Impairment

Varenicline pharmacokinetics were unchanged in subjects with mild renal impairment (estimated creatinine clearance > 50 mL/min and ≤ 80 mL/min). In subjects 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 those of healthy subjects receiving 1 mg twice daily [see *Dosage and Administration (2.2)*, *Use in Specific Populations (8.6)*]. Additionally, in subjects with ESRD, varenicline was efficiently removed by hemodialysis [see *Overdosage (10)*].

Hepatic Impairment

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

Drug-Drug Interactions

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 [*see below*]) 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 (e.g., cimetidine [*see below*]) may not necessitate a dose adjustment of CHANTIX as the increase in systemic exposure to CHANTIX 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 CHANTIX [*see Clinical Pharmacology (12.3)*]; therefore, a dose adjustment of CHANTIX would not be required.

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.

Metformin

When co-administered to 30 smokers, varenicline (1 mg twice daily) did not alter the steady-state pharmacokinetics of metformin (500 mg twice daily), 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 four times daily), 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 twice daily) did not alter the steady-state pharmacokinetics of digoxin administered as a 0.25 mg daily dose in 18 smokers.

Warfarin

Varenicline (1 mg twice daily) 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 [*see Drug Interactions (7.2)*].

Use with Other Drugs for Smoking Cessation

Bupropion: Varenicline (1 mg twice daily) did not alter the steady-state pharmacokinetics of bupropion (150 mg twice daily) in 46 smokers [*see Drug Interactions (7.1)*].

Nicotine replacement therapy (NRT): Although co-administration of varenicline (1 mg twice daily) and transdermal nicotine (21 mg/day) for up to 12 days did not affect nicotine pharmacokinetics, the incidence of adverse reactions was greater for the combination than for NRT alone [*see Drug Interactions (7.1)*].

13 NONCLINICAL TOXICOLOGY

13.1 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 (MRHD) 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 MRHD exposure based on AUC) and maximum dose (2 tumors, 15 mg/kg/day, 67 times the MRHD 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 MRHD exposure based on AUC at 1 mg twice daily). Maternal toxicity, characterized by a decrease in body weight gain, was observed at 15 mg/kg/day. 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. 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 MRHD exposure based on AUC at 1 mg twice daily).

14 CLINICAL STUDIES

The efficacy of CHANTIX 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 CHANTIX. 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 CHANTIX-treated patients enrolled in these studies, the completion rate was 65%. Except for the dose-ranging 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 patients enrolled in these trials were white (79–96%). All studies enrolled almost equal numbers of men and women. The average age of patients in these studies was 43 years. Patients on average had smoked about 21 cigarettes per day for an average of approximately 25 years. Patients set a date to stop smoking (target quit date) with dosing starting 1 week before this date.

Seven additional studies evaluated the efficacy of CHANTIX in patients with cardiovascular disease, in patients with chronic obstructive pulmonary disease [see *Clinical Studies (14.7)*], in patients instructed to select their quit date within days 8 and 35 of treatment [see *Clinical Studies (14.4)*], patients with major depressive disorder [see *Clinical Studies (14.8)*], patients who had made a previous attempt to quit smoking with CHANTIX, and either did not succeed in quitting or relapsed after treatment [see *Clinical Studies (14.6)*], in patients without or with a history of psychiatric disorder enrolled in a postmarketing neuropsychiatric safety outcome trial [see *Warnings and Precautions (5.1)*, *Clinical Studies (14.9)*], and in patients who were not able or willing to quit abruptly and were instructed to quit gradually [see *Clinical studies (14.5)*].

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.

14.1 Initiation of Abstinence

Study 1

This was a six-week dose-ranging study comparing CHANTIX to placebo. This study provided initial evidence that CHANTIX 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 patients compared CHANTIX 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. CHANTIX was given in two divided doses daily. Each dose of CHANTIX 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 patients receiving CHANTIX 1 mg per day (0.5 mg twice daily) and 51% of patients receiving 2 mg per day (1 mg twice daily) had CO-confirmed continuous abstinence during weeks 9 through 12 compared to 12% of patients in the placebo group (Figure 1). 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 patients examined the effect of a patient-directed dosing strategy of CHANTIX or placebo. After an initial one-week titration to a dose of 0.5 mg twice daily, patients could adjust their dosage as often as they wished between 0.5 mg once daily to 1 mg twice daily 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 twice daily; for slightly over half of the study participants, the modal dose selected was 1 mg/day or less.

Of the patients treated with CHANTIX, 40% had CO-confirmed continuous abstinence during weeks 9 through 12 compared to 12% in the placebo group. In addition, 29% of the CHANTIX 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 CHANTIX 2 mg per day, bupropion sustained-release (SR) 150 mg twice daily, and placebo. Patients were treated for 12 weeks and then were followed for 40 weeks post-treatment. The CHANTIX 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 SR dosage of 150 mg twice daily was achieved using a 3-day titration of 150 mg once daily. Study 4 enrolled 1022 patients and Study 5 enrolled 1023 patients. Patients inappropriate for bupropion treatment or patients who had previously used bupropion were excluded.

In Study 4, patients treated with CHANTIX 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 CHANTIX 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, patients treated with CHANTIX 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 CHANTIX 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.

Figure 1: Continuous Abstinence, Weeks 9 through 12

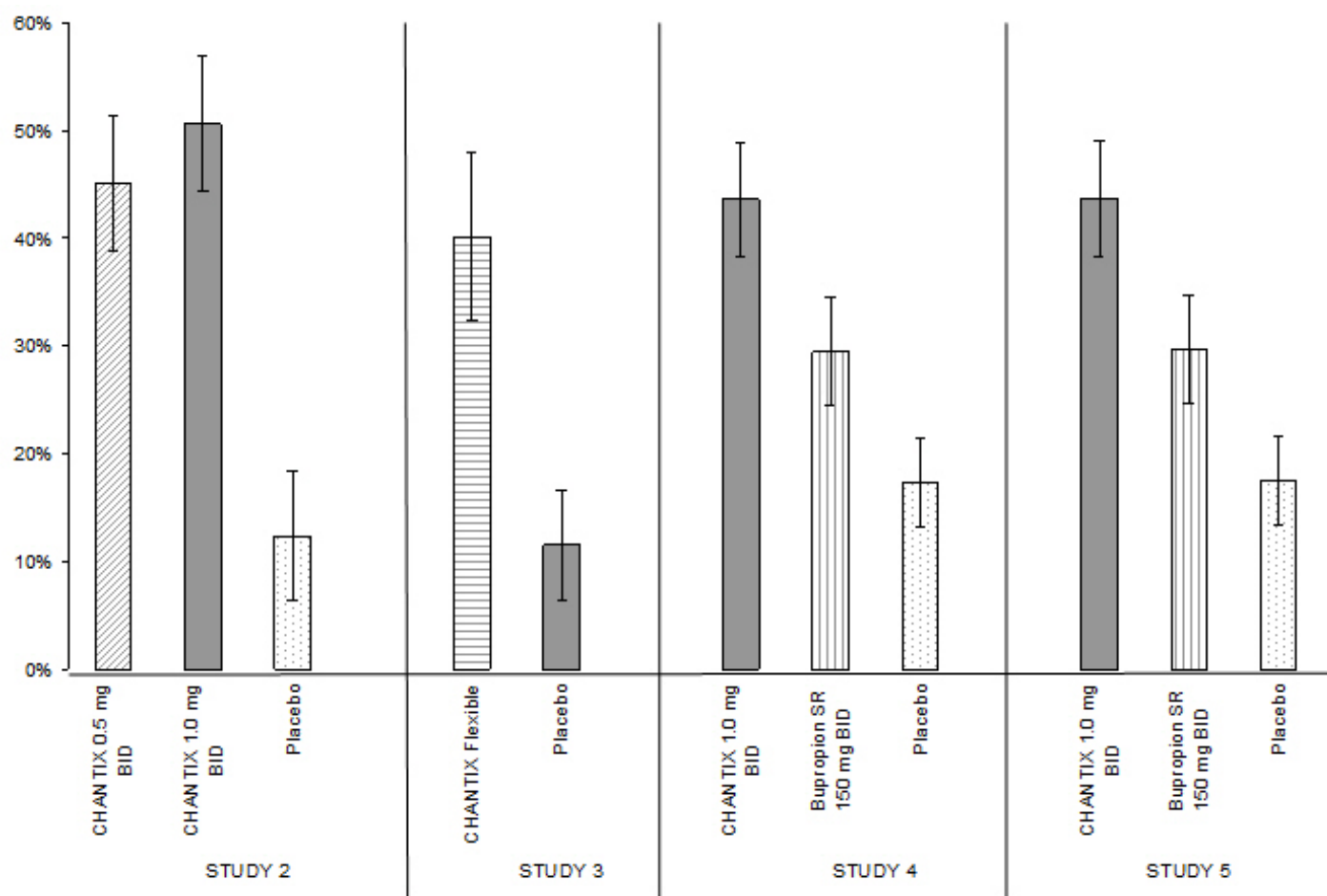


Table 4: Continuous Abstinence, Weeks 9 through 12 (95% confidence interval)

	CHANTIX 0.5 mg BID	CHANTIX 1 mg BID	CHANTIX 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%)

BID = twice daily

14.2 Urge to Smoke

Based on responses to the Brief Questionnaire of Smoking Urges and the Minnesota Nicotine Withdrawal scale "urge to smoke" item, CHANTIX reduced urge to smoke compared to placebo.

14.3 Long-Term Abstinence

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

Figure 2: Continuous Abstinence, Weeks 9 through 52

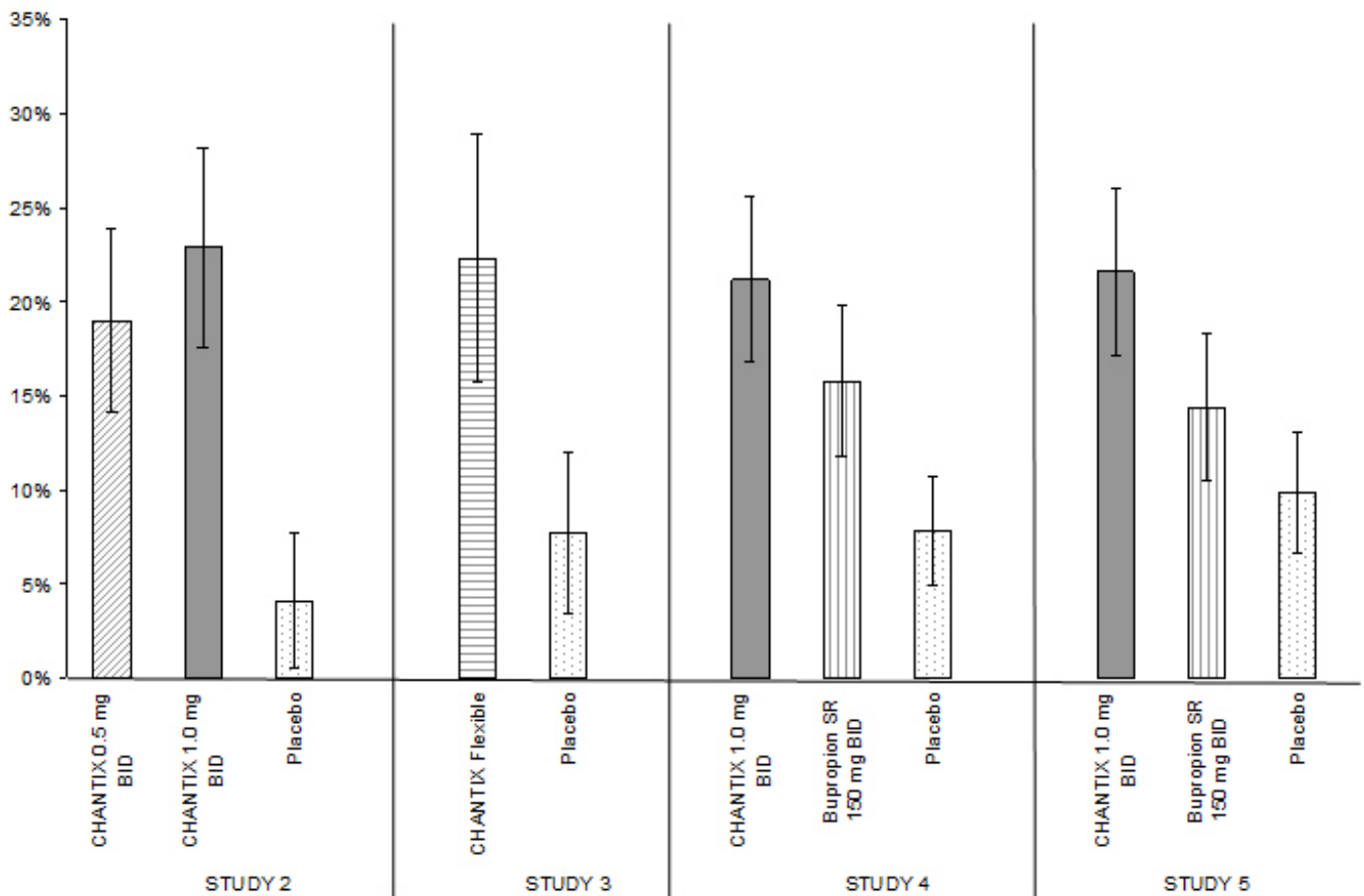


Table 5: Continuous Abstinence, Weeks 9 through 52 (95% confidence interval) Across Different Studies

	CHANTIX 0.5 mg BID	CHANTIX 1 mg BID	CHANTIX 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%)

BID = twice daily

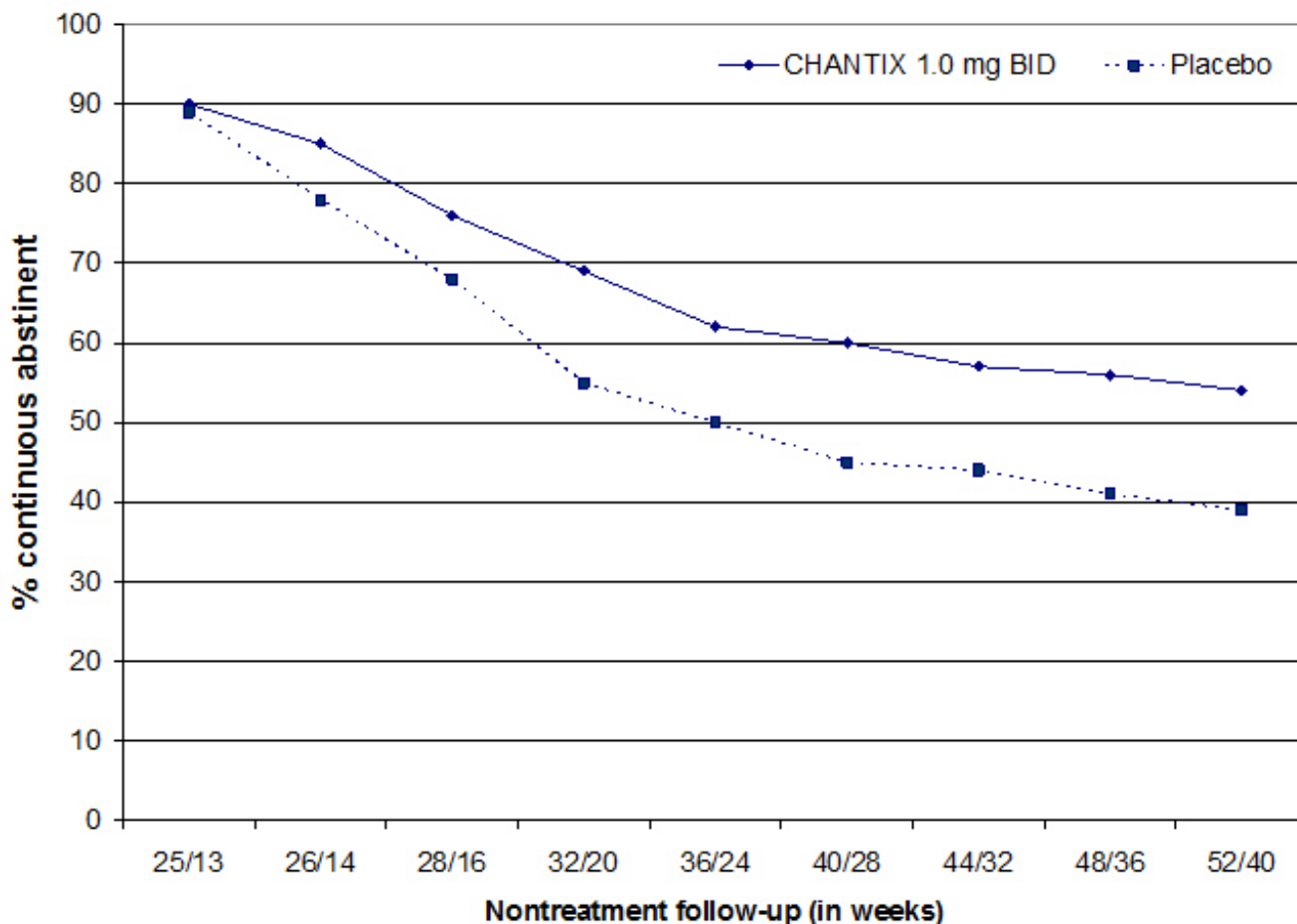
Study 6

This study assessed the effect of an additional 12 weeks of CHANTIX therapy on the likelihood of long-term abstinence. Patients in this study (N=1927) were treated with open-label CHANTIX 1 mg twice daily for 12 weeks. Patients who had stopped smoking for at least a week by Week 12 (N= 1210) were then randomized to double-blind treatment with CHANTIX (1 mg twice daily) 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 patients continuing treatment with CHANTIX (70%) than for patients switching to placebo (50%). Superiority to placebo was also maintained during 28 weeks post-treatment follow-up (CHANTIX 54% versus placebo 39%).

In Figure 3 below, the x-axis represents the study week for each observation, allowing a comparison of groups at similar times after discontinuation of CHANTIX; post-CHANTIX follow-up begins at Week 13 for the placebo group and Week 25 for the CHANTIX group. The y-axis represents the percentage of patients who had been abstinent for the last week of CHANTIX treatment and remained abstinent at the given timepoint.

Figure 3: Continuous Abstinence Rate during Nontreatment Follow-Up



14.4 Alternative Instructions for Setting a Quit Date

CHANTIX was evaluated in a double-blind, placebo-controlled trial where patients were instructed to select a target quit date between Day 8 and Day 35 of treatment. Subjects were randomized 3:1 to CHANTIX 1 mg twice daily (N=486) or placebo (N=165) for 12 weeks of treatment and followed for another 12 weeks post-treatment. Patients treated with CHANTIX had a superior rate of CO-confirmed abstinence during weeks 9 through 12 (54%) compared to patients treated with placebo (19%) and from weeks 9 through 24 (35%) compared to subjects treated with placebo (13%).

14.5 Gradual Approach to Quitting Smoking

CHANTIX was evaluated in a 52-week double-blind placebo-controlled study of 1,510 subjects who were not able or willing to quit smoking within four weeks, but were willing to gradually reduce their smoking over a 12 week period before quitting. Subjects were randomized to either CHANTIX 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 CHANTIX

had a significantly higher Continuous Abstinence Rate compared with placebo at weeks 15 through 24 (32% vs. 7%) and weeks 15 through 52 (24% vs. 6%).

14.6 Re-Treatment Study

CHANTIX was evaluated in a double-blind, placebo-controlled trial of patients who had made a previous attempt to quit smoking with CHANTIX, and either did not succeed in quitting or relapsed after treatment. Subjects were randomized 1:1 to CHANTIX 1 mg twice daily (N=249) or placebo (N=245) for 12 weeks of treatment and followed for 40 weeks post-treatment. Patients included in this study had taken CHANTIX 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 CHANTIX had a superior rate of CO-confirmed abstinence during weeks 9 through 12 (45%) compared to patients treated with placebo (12%) and from weeks 9 through 52 (20%) compared to subjects treated with placebo (3%).

Table 6: Continuous Abstinence (95% confidence interval), Re-Treatment Study

	Weeks 9 through 12		Weeks 9 through 52	
	CHANTIX 1 mg BID	Placebo	CHANTIX 1 mg BID	Placebo
Retreatment Study	45% (39%, 51%)	12% (8%, 16%)	20% (15%, 25%)	3% (1%, 5%)

BID = twice daily

14.7 Subjects with Cardiovascular and Chronic Obstructive Pulmonary Disease

CHANTIX was evaluated in a randomized, double-blind, placebo-controlled study of subjects aged 35 to 75 years with stable, documented cardiovascular disease (diagnoses other than, or in addition to, hypertension) that had been diagnosed for more than 2 months. Subjects were randomized to CHANTIX 1 mg twice daily (N=353) or placebo (N=350) for a treatment of 12 weeks and then were followed for 40 weeks post-treatment. Subjects treated with CHANTIX had a superior rate of CO-confirmed abstinence during weeks 9 through 12 (47%) compared to subjects treated with placebo (14%) and from week 9 through 52 (20%) compared to subjects treated with placebo (7%).

CHANTIX was evaluated in a randomized, double-blind, placebo-controlled study of subjects aged \geq 35 years with mild-to-moderate COPD with post-bronchodilator FEV₁/FVC <70% and FEV₁ \geq 50% of predicted normal value. Subjects were randomized to CHANTIX 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. Subjects treated with CHANTIX had a superior rate of CO-confirmed abstinence during weeks 9 through 12 (41%) compared to subjects treated with placebo (9%) and from week 9 through 52 (19%) compared to subjects treated with placebo (6%).

Table 7: Continuous Abstinence (95% confidence interval), Studies in Patients with Cardiovascular Disease (CVD) and Chronic Obstructive Pulmonary Disease (COPD)

	Weeks 9 through 12		Weeks 9 through 52	
	CHANTIX 1 mg BID	Placebo	CHANTIX 1 mg BID	Placebo
CVD Study	47% (42%, 53%)	14% (11%, 18%)	20% (16%, 24%)	7% (5%, 10%)
COPD Study	41% (34%, 47%)	9% (6%, 13%)	19% (14%, 24%)	6% (3%, 9%)

BID = twice daily

14.8 Subjects with Major Depressive Disorder

CHANTIX was evaluated in a randomized, double-blind, placebo-controlled study of subjects aged 18 to 75 years with major depressive disorder without psychotic features (DSM-IV TR). If on medication, subjects were to be on a stable antidepressant regimen for at least two months. If not on medication, subjects were to have experienced a major depressive episode in the past 2 years, which was successfully treated. Subjects were randomized to CHANTIX 1 mg twice daily (N=256) or placebo (N=269) for a treatment of 12 weeks and then followed for 40 weeks post-treatment. Subjects treated with CHANTIX had a superior rate of CO-confirmed abstinence during weeks 9 through 12 (36%) compared to subjects treated with placebo (16%) and from week 9 through 52 (20%) compared to subjects treated with placebo (10%).

Table 8: Continuous Abstinence (95% confidence interval), Study in Patients with Major Depressive Disorder (MDD)

	Weeks 9 through 12		Weeks 9 through 52	
	CHANTIX 1 mg BID	Placebo	CHANTIX 1 mg BID	Placebo
MDD Study	36% (30%, 42%)	16% (11%, 20%)	20% (15%, 25%)	10% (7%, 14%)

BID = twice daily

14.9 Postmarketing Neuropsychiatric Safety Outcome Trial

CHANTIX was evaluated in a randomized, double-blind, active and placebo-controlled trial that included subjects without a history of psychiatric disorder (non-psychiatric cohort, N=3912) and with a history of psychiatric disorder (psychiatric cohort, N=4003). Subjects aged 18–75 years, smoking 10 or more cigarettes per day were randomized 1:1:1:1 to CHANTIX 1 mg BID, bupropion SR 150 mg BID, nicotine replacement therapy patch (NRT) 21 mg/day with taper or placebo for a treatment period of 12 weeks; they were then followed for another 12 weeks post-treatment. [See Warnings and Precautions (5.1)]

A composite safety endpoint intended to capture clinically significant neuropsychiatric (NPS) adverse events included the following NPS adverse events: anxiety, depression, feeling abnormal, hostility, agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, irritability, suicidal ideation, suicidal behavior or completed suicide.

As shown in Table 9, the use of CHANTIX, bupropion, and NRT in the non-psychiatric cohort was not associated with an increased risk of clinically significant NPS adverse events compared with placebo. Similarly, in the non-psychiatric cohort, the use of CHANTIX was not associated with an increased risk of clinically significant NPS adverse events in the composite safety endpoint compared with bupropion or NRT.

Table 9. Number of Patients with Clinically Significant or Serious NPS Adverse Events by Treatment Group Among Patients without a History of Psychiatric Disorder

	CHANTIX (N=975) n (%)	Bupropion (N=968) n (%)	NRT (N=987) n (%)	Placebo (N=982) n (%)
Clinically significant NPS	30 (3.1)	34 (3.5)	33 (3.3)	40 (4.1)
Serious NPS	1 (0.1)	5 (0.5)	1 (0.1)	4 (0.4)
Psychiatric	1 (0.1)	2 (0.2)	2 (0.2)	1 (0.1)

hospitalizations	1 (0.1)	2 (0.2)	0 (0.0)	1 (0.1)
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As shown in Table 10, there were more clinically significant NPS adverse events reported in patients in the psychiatric cohort in each treatment group compared with the non-psychiatric cohort (Table 9). The incidence of events in the composite endpoint was higher for each of the active treatments compared to placebo: Risk Differences (RDs) (95%CI) vs placebo were 2.7% (-0.05, 5.4) for CHANTIX, 2.2% (-0.5, 4.9) for bupropion, and 0.4% (-2.2, 3.0) for NRT transdermal nicotine.

Table 10. Number of Patients with Clinically Significant or Serious NPS Adverse Events by Treatment Group Among Patients with a History of Psychiatric Disorder

	CHANTIX (N=1007) n (%)	Bupropion (N=1004) n (%)	NRT (N=995) n (%)	Placebo (N=997) n (%)
Clinically Significant NPS	123 (12.2)	118 (11.8)	98 (9.8)	95 (9.5)
Serious NPS	6 (0.6)	8 (0.8)	4 (0.4)	6 (0.6)
Psychiatric hospitalizations	5 (0.5)	8 (0.8)	4 (0.4)	2 (0.2)

There was one completed suicide, which occurred during treatment in a patient treated with placebo in the non-psychiatric cohort. There were no completed suicides reported in the psychiatric cohort.

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

Table 11: Continuous Abstinence (95% confidence interval), Study in Patients with or without a History of Psychiatric Disorder

	CHANTIX 1 mg BID	Bupropion SR 150 mg BID	NRT 21 mg/day with taper	Placebo
Weeks 9 through 12				
Non-Psychiatric Cohort	38% (35%, 41%)	26% (23%, 29%)	26% (24%, 29%)	14% (12%, 16%)
Psychiatric Cohort	29% (26%, 32%)	19% (17%, 22%)	20% (18%, 23%)	11% (10%, 14%)
Weeks 9 through 24				
Non-Psychiatric Cohort	25% (23%, 28%)	19% (16%, 21%)	18% (16%, 21%)	11% (9%, 13%)
Psychiatric Cohort	18% (16%, 21%)	14% (12%, 16%)	13% (11%, 15%)	8% (7%, 10%)

BID = twice daily

16 HOW SUPPLIED/STORAGE AND HANDLING

CHANTIX is supplied for oral administration in two strengths: a 0.5 mg capsular biconvex, white to off-white, film-coated tablet debossed with "Pfizer" on one side and "CHX 0.5" on the other side and a 1 mg capsular biconvex, light blue film-coated tablet debossed with "Pfizer" on one side and "CHX 1.0" on the other side. CHANTIX is supplied in the following package configurations:

	Description	NDC
Packs	Starting 2 week card: 0.5 mg × 11 tablets and 1 mg × 14 tablets	NDC 0069-0471-01
	Continuing 2 week card: 1 mg × 28 tablets	NDC 0069-0469-11
	Starting 4-week card: 0.5 mg × 11 tablets and 1 mg × 42 tablets	NDC 0069-0471-03
	Continuing 4-week card: 1 mg × 56 tablets	NDC 0069-0469-03
	Starting Month Box: 0.5 mg × 11 tablets and 1 mg × 42 tablets	NDC 0069-0471-02; NDC 0069-0471-03
	Continuing Month Box: 1 mg × 56 tablets	NDC 0069-0469-12; NDC 0069-0469-03
Bottles	0.5 mg - bottle of 56	NDC 0069-0468-56
	1 mg - bottle of 56	NDC 0069-0469-56

Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) (see USP Controlled Room Temperature).

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (*Medication Guide*)

Initiate Treatment and Continue to Attempt to Quit if Lapse

Instruct patients to set a date to quit smoking and to initiate CHANTIX treatment one week before the quit date. Alternatively, the patient can begin CHANTIX dosing and then set a date to quit smoking between days 8 and 35 of treatment. Encourage patients to continue to attempt to quit if they have early lapses after quit day [see *Dosage and Administration (2.1)*].

For patients who are sure that they are not able or willing to quit abruptly, a gradual approach to quitting smoking with CHANTIX may be considered. Patients should begin CHANTIX dosing and reduce smoking during the first 12 weeks of treatment, then quit by the end of that period and continue treatment for an additional 12 weeks for a total of 24 weeks [see *Dosage and Administration (2.1)*].

Encourage patients who are motivated to quit and who did not succeed in stopping smoking during prior CHANTIX therapy for reasons other than intolerability due to adverse events, or who relapsed after treatment to make another attempt with CHANTIX once factors contributing to the failed attempt have been identified and addressed [see *Dosage and Administration (2.1)*, *Clinical Studies (14.6)*].

How to Take

Advise patients that CHANTIX should be taken orally after eating, and with a full glass of water [see *Dosage and Administration (2.1)*].

Starting Week Dosage

Instruct patients on how to titrate CHANTIX, beginning at a dose of 0.5 mg/day. 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 [see *Dosage and Administration (2.1)*].

Continuing Weeks Dosage

Advise patients 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 [see *Dosage and Administration (2.1)*].

Dosage Adjustment for CHANTIX or Other Drugs

Inform patients that nausea and insomnia are side effects of CHANTIX and are usually transient;

however, advise patients that if they are persistently troubled by these symptoms, they should notify the prescribing physician so that a dose reduction can be considered.

Inform patients that some drugs may require dose adjustment after quitting smoking [*see Dosage and Administration (2.1)*].

Counseling and Support

Provide patients with educational materials and necessary counseling to support an attempt at quitting smoking [*see Dosage and Administration (2.1)*].

Neuropsychiatric Adverse Events

Inform patients that some patients have experienced changes in mood (including depression and mania), psychosis, hallucinations, paranoia, delusions, homicidal ideation, aggression, hostility, agitation, anxiety, and panic, as well as suicidal ideation and suicide when attempting to quit smoking while taking CHANTIX. Instruct patients to discontinue CHANTIX and contact a healthcare professional if they experience such symptoms [*see Warnings and Precautions (5.1), Adverse Reactions (6.2)*].

History of Psychiatric Illness

Encourage patients to reveal any history of psychiatric illness prior to initiating treatment.

Nicotine Withdrawal

Inform patients that quitting smoking, with or without CHANTIX, may be associated with nicotine withdrawal symptoms (including depression or agitation) or exacerbation of pre-existing psychiatric illness.

Seizures

Encourage patients to report any history of seizures or other factors that can lower seizure threshold. Instruct patients to discontinue CHANTIX and contact a healthcare provider immediately if they experience a seizure while on treatment [*see Warnings and Precautions (5.2)*].

Interaction with Alcohol

Advise patients to reduce the amount of alcohol they consume while taking CHANTIX until they know whether CHANTIX affects their tolerance for alcohol [*see Warnings and Precautions (5.3), Adverse Reactions (6.2)*].

Driving or Operating Machinery

Advise patients to use caution driving or operating machinery until they know how quitting smoking and/or varenicline may affect them [*see Warnings and Precautions (5.4)*].

Cardiovascular Events

Patients should be instructed to notify their healthcare providers of symptoms of new or worsening cardiovascular events and to seek immediate medical attention if they experience signs and symptoms of myocardial infarction or stroke [*see Warnings and Precautions (5.5), Adverse Reactions (6.1)*].

Somnambulism

Patients should be instructed to discontinue CHANTIX and notify their healthcare providers if they experience somnambulism [*see Warnings and Precautions (5.6)*].

Angioedema

Inform patients that there have been reports of angioedema, with swelling of the face, mouth (lip, gum, tongue) and neck (larynx and pharynx) that can lead to life-threatening respiratory compromise. Instruct patients to discontinue CHANTIX and immediately seek medical care if they experience these symptoms [*see Warnings and Precautions (5.7), Adverse Reactions (6.2)*].

Serious Skin Reactions

Inform patients that serious skin reactions, such as Stevens-Johnson Syndrome and erythema multiforme, were reported by some patients taking CHANTIX. Advise patients to stop taking CHANTIX at the first sign of rash with mucosal lesions or skin reaction and contact a healthcare provider immediately [see *Warnings and Precautions (5.8), Adverse Reactions (6.2)*].

Vivid, Unusual, or Strange Dreams

Inform patients that they may experience vivid, unusual or strange dreams during treatment with CHANTIX.

Pregnancy and Lactation

Patients who are pregnant or breastfeeding or planning to become pregnant should be advised of: the risks of smoking to a pregnant mother and her developing baby, the potential risks of CHANTIX use during pregnancy and breastfeeding, and the benefits of smoking cessation with and without CHANTIX. Advise breastfeeding women to monitor the infant for seizures and vomiting [see *Use in Specific Populations (8.1 and 8.2)*].

This product's label may have been updated. For full prescribing information, please visit www.pfizer.com



LAB- 0327-22.0

MEDICATION GUIDE CHANTIX® (CHANT-iks) (varenicline) Tablets

What is the most important information I should know about CHANTIX?

When you try to quit smoking, with or without CHANTIX, you may have symptoms that may be due to nicotine withdrawal, including:

- urge to smoke
- frustration
- restlessness
- depressed mood
- anger
- decreased heart rate
- trouble sleeping
- feeling anxious
- increased appetite
- irritability
- difficulty concentrating
- weight gain

Some people have even experienced suicidal thoughts when trying to quit smoking without medication. Sometimes quitting smoking can lead to worsening of mental health problems that you already have, such as depression.

Some people have had serious side effects while taking CHANTIX to help them quit smoking, including:

New or worse mental health problems, such as changes in behavior or thinking, aggression, hostility, agitation, depressed mood, or suicidal thoughts or actions. Some people had these symptoms when they began taking CHANTIX, and others developed them after several weeks of treatment, or after stopping CHANTIX. These symptoms happened more often in people who had a history of mental health problems before taking CHANTIX, than in people without a history of mental health problems.

Stop taking CHANTIX and call your healthcare provider right away if you, your family, or caregiver notice any of these symptoms. Work with your healthcare provider to decide whether you should continue to take CHANTIX. In many people, these symptoms went away after stopping CHANTIX, but in some people symptoms continued after stopping CHANTIX. It is important for you to

follow-up with your healthcare provider until your symptoms go away.

Before taking CHANTIX, tell your healthcare provider if you have ever had depression or other mental health problems. You should also tell your healthcare provider about any symptoms you had during other times you tried to quit smoking, with or without CHANTIX.

What is CHANTIX?

CHANTIX is a prescription medicine to help people stop smoking.

Quitting smoking can lower your chances of having lung disease, heart disease or getting certain types of cancer that are related to smoking.

It is not known if CHANTIX is safe and effective in children.

It is not known if CHANTIX is safe and effective when used with other stop smoking medicines.

Who should not take CHANTIX?

Do not take CHANTIX if you have had a serious allergic or skin reaction to CHANTIX. Symptoms may include:

- swelling of the face, mouth (tongue, lips, gums), throat or neck
- trouble breathing
- rash, with peeling skin
- blisters in your mouth

What should I tell my healthcare provider before taking CHANTIX?

See "**What is the most important information I should know about CHANTIX?**"

Before you take CHANTIX, tell your healthcare provider if you:

- use other treatments to quit smoking. Using CHANTIX with a nicotine patch may cause nausea, vomiting, headache, dizziness, upset stomach, and tiredness to happen more often than if you just use a nicotine patch alone.
- have kidney problems or get kidney dialysis. Your healthcare provider may prescribe a lower dose of CHANTIX for you.
- have a history of seizures
- drink alcohol
- have heart or blood vessel problems
- have any other medical conditions
- are pregnant or plan to become pregnant. It is not known if CHANTIX will harm your unborn baby.
- are breastfeeding. It is not known if CHANTIX passes into breast milk. If you breastfeed and take CHANTIX, monitor your baby for seizures as well as spitting up or vomiting more than normal.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins and herbal supplements. Your healthcare provider may need to change the dose of some of your medicines when you stop smoking.

You should not use CHANTIX while using other medicines to quit smoking. Tell your healthcare provider if you use other treatments to quit smoking.

Know the medicines you take. Keep a list of them with you to show your healthcare provider and pharmacist when you get a new medicine.

How should I take CHANTIX?

- There are 3 ways that you can use CHANTIX to help you quit smoking. Talk to your healthcare provider about the following 3 ways to use CHANTIX:
 - Choose a **quit date** when you will stop smoking. Start taking CHANTIX 1 week (7 days) before your **quit date**. Take CHANTIX for 12 weeks.
 - OR**
 - Start taking CHANTIX before you choose a **quit date**. Pick a date to quit smoking that is between days 8 and 35 of treatment. Take CHANTIX for 12 weeks.
 - OR**
 - If you are sure that you are not able or willing to quit smoking right away, start taking

CHANTIX and reduce smoking during the first 12 weeks of treatment, as follows:

Weeks 1 through 4	Reduce your smoking to reach one-half of your starting daily number of cigarettes. Example: If you usually smoke 20 cigarettes each day, reduce your smoking to 10 cigarettes each day during weeks 1 through 4.
Weeks 5 through 8	Reduce your smoking to reach one-quarter of your starting daily number of cigarettes. Example: If you usually smoked 20 cigarettes each day, reduce your smoking to 5 cigarettes each day during weeks 5 through 8.
Weeks 9 through 12	Keep reducing your smoking until you are no longer smoking (you reach zero cigarettes each day).

Aim to quit by the end of the 12th week of treatment, or sooner if you feel ready. Continue to take CHANTIX for another 12 weeks, for a total of 24 weeks of treatment.

Starting CHANTIX before your **quit date** gives CHANTIX time to build up in your body. You can keep smoking during this time. Take CHANTIX exactly as prescribed by your healthcare provider.

- CHANTIX comes as a white tablet (0.5 mg) and a blue tablet (1 mg). You start with the white tablet and then usually go to the blue tablet. See the chart below for dosing instructions for adults.

Day 1 to Day 3	<ul style="list-style-type: none"> ◦ <u>White</u> tablet (0.5 mg) ◦ Take 1 tablet each day
Day 4 to Day 7	<ul style="list-style-type: none"> ◦ <u>White</u> tablet (0.5 mg) ◦ Take 1 in the morning and 1 in the evening
Day 8 to end of treatment	<ul style="list-style-type: none"> ◦ <u>Blue</u> tablet (1 mg) ◦ Take 1 in the morning and 1 in the evening

- Make sure that you try to stop smoking on your quit date. If you slip-up and smoke, try again. Some people need to take CHANTIX for a few weeks for CHANTIX to work best.
- Most people will take CHANTIX for up to 12 weeks. If you have completely quit smoking by 12 weeks, your healthcare provider may prescribe CHANTIX for another 12 weeks to help you stay cigarette-free.
- Take CHANTIX after eating and with a full glass (8 ounces) of water.
- This dosing schedule may not be right for everyone. Talk to your healthcare provider if you are having side effects such as nausea, strange dreams, or sleep problems. Your healthcare provider may want to reduce your dose.
- If you miss a dose of CHANTIX, take it as soon as you remember. If it is almost time for your next dose, skip the missed dose. Just take your next dose at your regular time.

What should I avoid while taking CHANTIX?

- Use caution when driving or operating machinery until you know how CHANTIX affects you. CHANTIX may make you feel sleepy, dizzy, or have trouble concentrating, making it hard to drive or perform other activities safely.
- Decrease the amount of alcoholic beverages that you drink during treatment with CHANTIX until you know if CHANTIX affects your ability to tolerate alcohol. Some people have experienced the following when drinking alcohol during treatment with CHANTIX:
 - increased drunkenness
 - unusual or sometimes aggressive behavior

(intoxication)

◦ no memory of things that have happened

What are the possible side effects of CHANTIX?

Serious side effects of CHANTIX may include:

- See "**What is the most important information I should know about CHANTIX?**"
- **Seizures.** Some people have had seizures during treatment with CHANTIX. In most cases, the seizures have happened during the first month of treatment with CHANTIX. If you have a seizure during treatment with CHANTIX, stop taking CHANTIX and contact your healthcare provider right away.
- **New or worse heart or blood vessel (cardiovascular) problems,** mostly in people, who already have cardiovascular problems. Tell your healthcare provider if you have any changes in symptoms during treatment with CHANTIX.
Get emergency medical help right away if you have any of the following symptoms of a heart attack, including:
 - chest discomfort (uncomfortable pressure, squeezing, fullness or pain) that lasts more than a few minutes, or that goes away and comes back
 - pain or discomfort in one or both arms, back, neck, jaw or stomach
 - shortness of breath, sweating, nausea, vomiting, or feeling lightheaded associated with chest discomfort
- **Sleepwalking** can happen with CHANTIX, and can sometimes lead to behavior that is harmful to you or other people, or to property. Stop taking CHANTIX and tell your healthcare provider if you start sleepwalking.
- **Allergic reactions** can happen with CHANTIX. Some of these allergic reactions can be life-threatening.
- **Serious skin reactions,** including rash, swelling, redness, and peeling of the skin. Some of these skin reactions can become life-threatening.

Stop taking CHANTIX and get medical help right away if you have any of the following symptoms:

- swelling of the face, mouth (tongue, lips, and gums), throat or neck
- trouble breathing
- rash with peeling skin
- blisters in your mouth

The most common side effects of CHANTIX include:

- nausea
- sleep problems (trouble sleeping or vivid, unusual, or strange dreams)
- constipation
- gas
- vomiting

Tell your healthcare provider about side effects that bother you or that do not go away.

These are not all the side effects of CHANTIX. Ask your healthcare provider or pharmacist for more information.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store CHANTIX?

- Store CHANTIX at room temperature, between 68°F to 77°F (20°C to 25°C).
- **Keep CHANTIX and all medicines out of the reach of children.**

General information about the safe and effective use of CHANTIX

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use CHANTIX for a condition for which it was not prescribed. Do not give your CHANTIX to other people, even if they have the same symptoms that you have. It may harm them. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about CHANTIX that is written for healthcare professionals.

For more information about CHANTIX and tips on how to quit smoking, go to www.CHANTIX.com or call 1-877-242-6849.

If you are motivated to quit smoking and did not succeed during prior CHANTIX treatment for reasons other than side effects, or if you returned to smoking after treatment, speak with your healthcare provider about whether another course of CHANTIX therapy may be right for you.

What are the ingredients in CHANTIX?

Active ingredient: varenicline tartrate

Inactive ingredients: microcrystalline cellulose, anhydrous dibasic calcium phosphate, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, Opadry® White (for 0.5 mg), Opadry® Blue (for 1 mg), and Opadry® Clear.

Distributed by



Pfizer Labs

Division of Pfizer Inc, NY, NY 10017

December 2016

LAB-0328-15.0

Repackaging Information

Please reference the **How Supplied** section listed above for a description of individual tablets. This drug product has been received by Aphenia Pharma - TN in a manufacturer or distributor packaged configuration and repackaged in full compliance with all applicable cGMP regulations. The package configurations available from Aphenia are listed below:

Count	1 mg
4200	43353-899-05

Store between 20°-25°C (68°-77°F). See USP Controlled Room Temperature. Dispense in a tight light-resistant container as defined by USP. Keep this and all drugs out of the reach of children.

Repackaged by:



Cookeville, TN 38506

20171218JH

PRINCIPAL DISPLAY PANEL - 1 mg

NDC 43353-899 - Varenicline (Chantix) 1 mg - Rx Only



CHANTIX

varenicline tartrate tablet, film coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:43353-899(NDC:0069-0469)
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
VARENICLINE TARTRATE (UNII: 82269ASB48) (VARENICLINE - UNII:W6HS99O8ZO)	VARENICLINE	1 mg

Inactive Ingredients

Ingredient Name	Strength
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
ANHYDROUS DIBASIC CALCIUM PHOSPHATE (UNII: L11K75P92J)	
CROSCARMELOSE SODIUM (UNII: M28OL1HH48)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
HYPROMELLOSE, UNSPECIFIED (UNII: 3NXW29V3WO)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
POLYETHYLENE GLYCOL, UNSPECIFIED (UNII: 3WJQ0SDW1A)	
FD&C BLUE NO. 2 (UNII: L06K8R7DQK)	

Product Characteristics

Color	BLUE (light blue)	Score	no score
Shape	OVAL (Capsular)	Size	10 mm
Flavor		Imprint Code	Pfizer;CHX;1;0
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:43353-899-05	4200 in 1 BOTTLE; Type 0: Not a Combination Product	03/07/2014	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA021928	05/10/2006	

Labeler - Aphenia Pharma Solutions - Tennessee, LLC (128385585)

Establishment

Name	Address	ID/FEI	Business Operations
Aphenia Pharma Solutions - Tennessee, LLC		128385585	REPACK(43353-899)

Revised: 12/2017

Aphenia Pharma Solutions - Tennessee, LLC