

## 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  
Initial U.S. Approval: 2006

### WARNING: SERIOUS NEUROPSYCHIATRIC EVENTS See full prescribing information for complete boxed warning.

- Serious neuropsychiatric events have been reported in patients taking CHANTIX. (5.1 and 6.2)
- Advise patients and caregivers that the patient should stop taking CHANTIX and contact a healthcare provider immediately if agitation, hostility, 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 while taking CHANTIX or shortly after discontinuing CHANTIX. (5.1 and 6.2)
- Weigh the risks of CHANTIX against benefits of its use. CHANTIX has been demonstrated to increase the likelihood of abstinence from smoking for as long as one year compared to treatment with placebo. The health benefits of quitting smoking are immediate and substantial. (5.1 and 6.2)

### RECENT MAJOR CHANGES

Warnings and Precautions  
Neuropsychiatric Symptoms and Suicidality (5.1) 01/2013  
Cardiovascular Events (5.4) 12/2012

### 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)
- Renal impairment: Reduce the dose in patients with severe renal impairment (estimated creatinine clearance <30 mL/min). (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)

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

- WARNINGS AND PRECAUTIONS-----
- **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. (5.2 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. (5.3 and 6.2)
  - **Cardiovascular events:** A meta-analysis of 15 clinical trials, including a trial in patients with stable cardiovascular 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 health care providers of new or worsening cardiovascular symptoms and to seek immediate medical attention if they experience signs and symptoms of myocardial infarction or stroke. (5.4 and 6.1)
  - **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. (5.5)
  - **Nausea:** Nausea is the most common adverse reaction (up to 30% incidence rate). Dose reduction may be helpful. (5.6)

-----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](http://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: Pharmacokinetics or pharmacodynamics of certain drugs may be altered due to smoking cessation with CHANTIX, necessitating dose adjustment. (7.2)

- USE IN SPECIFIC POPULATIONS-----
- **Pregnancy:** CHANTIX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (8.1)
  - **Nursing Mothers:** Discontinue drug or nursing taking into consideration importance of drug to mother (8.3)
  - **Pediatric Use:** Safety and effectiveness not established (8.4)
  - **Renal Impairment:** Dosage adjustment is required for severe renal impairment. (2.2, 8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

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## FULL PRESCRIBING INFORMATION

Day 8 – end of treatment:	1 mg twice daily
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### WARNING: SERIOUS NEUROPSYCHIATRIC EVENTS

Serious neuropsychiatric events including, but not limited to, depression, suicidal ideation, suicide attempt, and completed suicide have been reported in patients taking CHANTIX. Some reported cases may have been complicated by the symptoms of nicotine withdrawal in patients who stopped smoking. Depressed mood may be a symptom of nicotine withdrawal. Depression, rarely including suicidal ideation, has been reported in smokers undergoing a smoking cessation attempt without medication. However, some of these symptoms have occurred in patients taking CHANTIX who continued to smoke.

All patients being treated with CHANTIX should be observed for neuropsychiatric symptoms including changes in behavior, hostility, agitation, depressed mood, and suicide-related events, including ideation, behavior, and attempted suicide. These symptoms, as well as worsening of pre-existing psychiatric illness and completed suicide, have been reported in some patients attempting to quit smoking while taking CHANTIX in the postmarketing experience. When symptoms were reported, most were during CHANTIX treatment, but some were following discontinuation of CHANTIX therapy.

These events have occurred in patients with and without pre-existing psychiatric disease. Patients with serious psychiatric illness such as schizophrenia, bipolar disorder, and major depressive disorder did not participate in the premarketing studies of CHANTIX, and the safety and efficacy of CHANTIX in such patients has not been established.

Advise patients and caregivers that the patient should stop taking CHANTIX and contact a healthcare provider immediately if agitation, hostility, 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. In many postmarketing cases, resolution of symptoms after discontinuation of CHANTIX was reported, although in some cases the symptoms persisted; therefore, ongoing monitoring and supportive care should be provided until symptoms resolve.

The risks of CHANTIX should be weighed against the benefits of its use. CHANTIX has been demonstrated to increase the likelihood of abstinence from smoking for as long as one year compared to treatment with placebo. The health benefits of quitting smoking are immediate and substantial. [see Warnings and Precautions (5.1) and Adverse Reactions (6.2)]

## 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 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:

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.

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

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 <30 mL/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 a day. For patients with end-stage renal disease undergoing hemodialysis, a maximum dose of 0.5 mg once daily may be administered if tolerated [see Use in Specific Populations (8.6) and 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 Symptoms and Suicidality

Serious neuropsychiatric symptoms have been reported in patients being treated with CHANTIX [see Boxed Warning and Adverse Reactions (6.2)]. These postmarketing reports have included changes in mood (including depression and mania), psychosis, hallucinations, paranoia, delusions, homicidal ideation, hostility, agitation, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed suicide. Some reported cases may have been complicated by the symptoms of nicotine withdrawal in patients who stopped smoking. Depressed mood may be a symptom of nicotine withdrawal. Depression, rarely including suicidal ideation, has been reported in smokers undergoing a smoking cessation attempt without medication. However, some of these symptoms have occurred in patients taking CHANTIX who continued to smoke. When symptoms were reported, most were during CHANTIX treatment, but some were following discontinuation of CHANTIX therapy.

These events have occurred in patients with and without pre-existing psychiatric disease; some patients have experienced worsening of their psychiatric illnesses. All patients being treated with CHANTIX should be observed for neuropsychiatric symptoms or worsening of pre-existing psychiatric illness. Patients with serious psychiatric illness such as schizophrenia, bipolar disorder, and major depressive disorder did not participate in the premarketing studies of CHANTIX, and the safety and efficacy of CHANTIX in such patients has not been established. Limited data

Advise patients and caregivers that the patient should stop taking CHANTIX and contact a healthcare provider immediately if agitation, depressed mood, changes in behavior or thinking that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behavior. In many postmarketing cases, resolution of symptoms after discontinuation of CHANTIX was reported, although in some cases the symptoms persisted, therefore, ongoing monitoring and supportive care should be provided until symptoms resolve.

The risks of CHANTIX should be weighed against the benefits of its use. CHANTIX has been demonstrated to increase the likelihood of abstinence from smoking for as long as one year compared to treatment with placebo. The health benefits of quitting smoking are immediate and substantial.

### 5.2 Angioedema and Hypersensitivity Reactions

There have been postmarketing reports of hypersensitivity reactions including angioedema in patients treated with CHANTIX [see *Adverse Reactions (6.2)*, and *Patient Counseling Information (17.10)*]. 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.

### 5.3 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.

### 5.4 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 *Clinical Trials Experience (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 (%)
<b>Mortality (Cardiovascular &amp; All-cause up to 52 wks)</b>		
Cardiovascular death	1 (0.3)	2 (0.6)
All-cause mortality	2 (0.6)	5 (1.4)
<b>Nonfatal Cardiovascular Events (rate on CHANTIX &gt; Placebo)</b>		
<u>Up to 30 days after treatment</u>		
Nonfatal myocardial infarction	4 (1.1)	1 (0.3)
Nonfatal Stroke	2 (0.6)	0 (0)
<u>Beyond 30 days after treatment &amp; up to 52 weeks</u>		
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  $\geq 12$  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

[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
<b>Hazard Ratio (95% CI)</b>		
	1.95 (0.79, 4.82)	
<b>Rate Difference per 1,000 patient-years (95% CI)</b>		
	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 health care 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.

### 5.5 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.

### 5.6 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 symptoms and suicidality [see *Boxed Warning and Warnings and Precautions (5.1)*]

- Serious skin reactions [see Warnings and Precautions (5.3)]
- Accidental injury [see Warnings and Precautions (5.5)]

In the placebo-controlled 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 (5.6)].

Table 3 shows the adverse events for CHANTIX and placebo in the 12-week fixed dose 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 ≥ 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 ≥ 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 ≥ 5% of patients in the 1 mg BID CHANTIX Group and more commonly than placebo and PT ≥ 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
<b>GASTROINTESTINAL (GI)</b>			
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
<b>PSYCHIATRIC DISORDERS</b>			
Sleep Disorder/Disturbances			
Insomnia **	19	18	13
Abnormal dreams	9	13	5
Sleep disorder	2	5	3
Nightmare	2	1	0
<b>NERVOUS SYSTEM</b>			
Headaches			

<b>NEC</b>			
Dysgeusia	8	5	4
Somnolence	3	3	2
Lethargy	2	1	0
<b>GENERAL DISORDERS</b>			
General Disorders NEC			
Fatigue/Malaise/Asthenia	4	7	6
<b>RESPIR/THORACIC/MEDI AST</b>			
Respiratory Disorders NEC			
Rhinorrhea	0	1	0
Dyspnea	2	1	1
Upper Respiratory Tract Disorder	7	5	4
<b>SKIN/SUBCUTANEOUS TISSUE</b>			
Epidermal and Dermal Conditions			
Rash	1	3	2
Pruritis	0	1	1
<b>METABOLISM &amp; NUTRITION</b>			
Appetite/General Nutrit. 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 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 clinical trials. The listing does not include those events already listed in the previous tables or elsewhere in labeling, those events for which a drug cause was remote, those events which were so general as to be uninformative, and those events reported only once which did not have a substantial probability of being acutely life-threatening.

**Blood and Lymphatic System Disorders.** *Infrequent:* anemia, lymphadenopathy. *Rare:* leukocytosis, splenomegaly, thrombocytopenia.

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

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

**Endocrine Disorders.** *Infrequent:* thyroid gland disorders.

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

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

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

**Hepatobiliary Disorders.** *Infrequent:* gall bladder disorder.

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

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

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

**Nervous System Disorders.** *Frequent:* disturbance in attention, dizziness, sensory disturbance. *Infrequent:* amnesia, migraine, parosmia, psychomotor hyperactivity, restless legs syndrome, syncope, tremor. *Rare:* balance disorder, cerebrovascular accident, convulsion, dysarthria, facial palsy, mental impairment, multiple sclerosis, nystagmus, psychomotor skills impaired.

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

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

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

Respiratory, Thoracic and Mediastinal Disorders. *Frequent:* epistaxis, respiratory disorders. *Infrequent:* asthma. *Rare:* pleurisy, pulmonary embolism.

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

Vascular Disorders. *Frequent:* hot flush. *Infrequent:* 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 with stable cardiovascular disease and (4) a trial conducted in patients with stable schizophrenia or schizoaffective disorder.

Adverse events in the trial of patients with COPD and in the alternative quit date instruction trial were quantitatively and qualitatively similar to those observed in premarketing studies.

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 post-marketing 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.

## 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 *Boxed Warning, Warnings and Precautions (5.1)*]. Smoking cessation with or without treatment is associated with nicotine withdrawal symptoms and the exacerbation of underlying psychiatric illness. Not all patients had known pre-existing psychiatric illness and not all had discontinued smoking.

There have been reports of hypersensitivity reactions, including angioedema [see *Warnings and Precautions (5.2)*].

There have also been reports of serious skin reactions, including Stevens-Johnson Syndrome and erythema multiforme, in patients taking CHANTIX [see *Warnings and Precautions (5.3)*].

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.

## 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

Pregnancy Category C.

There are no adequate and well-controlled studies of CHANTIX use in pregnant women. In animal studies, CHANTIX caused decreased fetal weights, increased auditory startle response, and decreased fertility in offspring. CHANTIX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In reproductive and developmental toxicity studies, pregnant rats and rabbits received varenicline succinate during organogenesis at oral doses up to 15 and 30 mg/kg/day, respectively. These exposures were 36 (rats) and 50 (rabbits) times the human exposure (based on AUC) at the maximum recommended human dose (MRHD) of 1 mg twice daily. While no fetal structural abnormalities occurred in either species, reduced fetal weights occurred in rabbits at the highest dose (exposures 50 times the human exposure at the MRHD based on AUC). Fetal weight reduction did not occur at animal 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. These resulted in exposures up to 36 times the human exposure (based on AUC) at the MRHD of 1 mg twice daily. Decreased fertility and increased auditory startle response occurred in offspring.

### 8.3 Nursing Mothers

It is not known whether CHANTIX is excreted in human milk. In animal

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