CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

021928Orig1s038

Trade Name: CHANTIX

Generic or Proper Name: varenicline tartrate

Sponsor: Pfizer, Inc.

Approval Date: 09/19/2014

Indication: CHANTIX is a nicotinic receptor partial agonist indicated for use as an aid to smoking cessation treatment.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021928/S-038

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021928/S-038

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021928/S-032, S-036, S-038

SUPPLEMENT APPROVAL

Pfizer, Inc.
235 E. 42nd Street
New York, NY 10017

Attention: Lilya I. Donohew, PhD
Senior Director, Worldwide Regulatory Affairs

Dear Dr. Donohew:

Please refer to your Supplemental New Drug Applications (sNDAs) dated and received October 24, 2013(S-032), April 8, 2014 (S-036), and September 3, 2014 (S-038), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Chantix (varenicline) Tablets; 0.5 mg and 1 mg.

We acknowledge receipt of your amendments dated November 8, and December 20, 2013, April 30, and September 18, 2014 (S-032), April 29, May 2, 5, and 8, August 1, and September 18, 2014 (S-036), and September 3, and 18, 2014 (S-038), and your proposed risk evaluation and mitigation strategy (REMS) modification dated November 8, 2013 (S-032) and September 3, 2014 (S-038).

We also refer to our letter dated August 6, 2014, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for Chantix. This information pertains to the risk of seizures and the potentiation of the intoxicating effects of alcohol.

Finally we refer you to our September 4, 2013, and August 6, 2014, letters notifying you, under section 505-1(g)(4)(B) of the FDCA, that your REMS must be modified based on findings from your 18-month REMS assessment and the new safety information described above.

Supplement S-032 proposes revisions to the **DRUG INTERACTIONS** section of the Package Insert regarding a potential interaction between alcohol and varenicline and includes a proposed modification to the approved risk evaluation and mitigation strategy (REMS), including revisions to the Medication Guide and revisions to the Chantix REMS goal.

Supplement S-036 proposes changes to the Package Insert based on meta-analyses of varenicline clinical trials and published observational studies pertaining to serious neuropsychiatric events.

Supplement S-038 proposes revisions to the labeling for Chantix. The agreed upon changes to the language included in our August 6, 2014, letter are included in the appended labeling text.

S-038 also includes additional proposed modifications to the approved risk evaluation and mitigation strategy (REMS), comprising further revisions to the Medication Guide as well as revisions to the Chantix REMS goal.

APPROVAL & LABELING

We have completed our review of these supplemental applications, as amended, and they are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling(text for the package insert and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

The REMS for Chantix (varenicline) was originally approved on October 19, 2009, and the most recent modification was approved on July 22, 2011. The REMS consists of a Medication Guide and a timetable for submission of assessments of the REMS. Your proposed modifications to the REMS consist of revisions to the Medication Guide to describe the risk of seizures and the potentiation of the intoxicating effects of alcohol, and revise the "What is the most important

information I should know about CHANTIX" section of the Medication Guide as well as other sections of the Medication Guide so as to furnish adequate information for the safe and effective use of the drug. In addition, the proposed modification includes revisions to the Chantix REMS goal to focus only on neuropsychiatric risks.

Your proposed modified REMS, submitted on September 3, 2014, and appended to this letter, is approved.

The modified REMS consists of a Medication Guide and a timetable for submission of assessments of the REMS.

The timetable for submission of assessments of the REMS will remain the same as that approved on October 19, 2009.

There are no changes to the REMS assessment plan described in our October 19, 2009, letter.

In addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

NDA 021928 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY)

Prominently identify the submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

NDA 021928 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 021928
PROPOSED REMS MODIFICATION

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 021928
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions.

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Ayanna Augustus, PhD, RAC, Sr. Regulatory Project Manager, at (301) 796-3980.

Sincerely,

{See appended electronic signature page}

Judith A. Racoosin, MD, MPH
Deputy Director for Safety
Division of Anesthesia, Analgesia and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling
REMS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JUDITH A RACOOSIN
09/19/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021928/S-038

LABELING

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)	09/2014
Seizures (5.2)	09/2014
Interaction with Alcohol (5.3)	09/2014

----------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)

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

----------WARNINGS AND PRECAUTIONS----------
- **Seizure**s: 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 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 5 and 6.1)
- **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. (5.6 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. (5.7 and 6.2)
- **Nausea:** Nausea is the most common adverse reaction (up to 30% incidence rate). Dose reduction may be helpful. (5.8)

----------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: 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

Revised: 09/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

**Sections or subsections omitted from the full prescribing information are not listed.*

FULL PRESCRIBING INFORMATION

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.

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:

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.

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. Limited safety data are available from post-marketing smoking cessation studies in two patient groups: 1) patients with major depressive disorder, and 2) patients with stable schizophrenia or schizoaffective disorder *[see Adverse Reactions (6.1)]*.

Some reported neuropsychiatric events, including unusual and sometimes aggressive behavior directed to oneself or others, may have been worsened by concomitant use of alcohol *[see Interaction with Alcohol (5.3), Adverse Reactions (6.2)]*.

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.

Since the initial signal of neuropsychiatric symptoms and suicidality emerged, additional analyses and studies have been conducted to further evaluate this association.

Analyses of clinical trials

A meta-analysis of 5 randomized, double blind, placebo controlled trials, including 1907 patients (1130 CHANTIX, 777 placebo) was conducted to assess suicidal ideation and behavior as reported on the Columbia-Suicide Severity Rating Scale (C SSRS). This meta-analysis included one trial (N=127) in patients with a history of schizophrenia or schizoaffective disorder and another trial (N=525) in patients with a history of depression. The results showed no increase in the incidence of suicidal ideation and/or behavior in patients treated with CHANTIX compared to patients treated with placebo, with a Risk Ratio (RR) of 0.79 (95% Confidence Interval [CI]: 0.46 , 1.36), as shown in Table 1. Forty-eight (48) of the 55 patients who reported suicidal ideation or behavior (24 CHANTIX, 24 placebo) were observed in the two trials that enrolled patients with a history of schizophrenia, schizoaffective disorder, or depression. Few events were observed in the other three trials (4 CHANTIX, 3 placebo).

Table 1. Number of patients and Risk Ratio for Suicidal Ideation and/or Behavior Reported on C-SSRS from a Meta-Analysis of 5 Clinical Trials Comparing CHANTIX to Placebo

	CHANTIX (N=1130)	**Placebo** (N=777)
Patients with Suicidal ideation and/or behavior* [n (%)]**	28 (2.5)	27 (3.5)
Patient-years of exposure	325	217
Risk Ratio # (RR; 95% CI)	0.79 (0.46, 1.36)	

* Of the events, one patient in each treatment arm reported suicidal behavior
** Patients with events up to 30 days after treatment**;** % are not weighted by study
# RR of incidence rates per 100 patient years

A pooled analysis of 18 double-blind, randomized, placebo-controlled clinical trials, which includes the 5 trials that collected C-SSRS described in Table 1, was conducted to assess the psychiatric safety of CHANTIX. This pooled analysis included 8521 patients (5072 CHANTIX, 3449 placebo), some of whom had psychiatric conditions at baseline. Table 2 describes the most frequently (≥ 1%) reported adverse events related to psychiatric safety. The results showed a similar incidence of common psychiatric events in patients treated with CHANTIX compared to patients treated with placebo.

Table 2. Psychiatric Adverse Events Occurring in ≥ 1% of Patients from Pooled Analysis of 18 Clinical Trials

	CHANTIX (N=5072)	**Placebo** (N=3449)
Anxiety disorders and symptoms	253 (5.0)	206 (6.0)
Depressed mood disorders and disturbances	179 (3.5)	108 (3.1)
Mood disorders and disturbances NEC*	116 (2.3)	53 (1.5)

* NEC = Not Elsewhere Classified
Counts (percentages) corresponds to the number of patients reporting the event

Observational Studies

Four observational studies, each including 10,000 to 30,000 users of CHANTIX in the adjusted analyses, compared the risk of selected serious neuropsychiatric events (neuropsychiatric hospitalizations, fatal and non-fatal self-harm), between CHANTIX users and prescription NRT or bupropion users. All studies were retrospective cohort studies and included patients with and without a psychiatric history.

Two of the studies found no difference in risk of neuropsychiatric hospitalizations between CHANTIX users and nicotine patch users (Hazard Ratio [HR] 1.14; 95% Confidence Interval [CI]: 0.56–2.34 in the first study, and 0.76; 95% CI: 0.40-1.46 in the second study). However, neither study validated the diagnostic codes used to identify outcomes against medical records. A third study reported no difference in risk of psychiatric adverse events diagnosed during an emergency department visit or inpatient admission between CHANTIX users and bupropion users (HR 0.85; 95% CI: 0.55-1.30). Bupropion has also been associated with neuropsychiatric adverse events. A fourth study examined risk of fatal and non-fatal self-harm in users of CHANTIX compared to users of NRT. Although the occurrence of detected suicide was rare during the three months after patients initiated any drug treatment (two cases in 31,260 CHANTIX users and six cases in 81,545 NRT users), this study has important limitations. Most importantly, these data were captured following public awareness of reports of neuropsychiatric adverse events in CHANTIX users. CHANTIX users had fewer comorbid conditions that could put them at risk for neuropsychiatric adverse events, suggesting that patients with a history of neuropsychiatric illness were preferentially prescribed NRT, and healthier patients were preferentially prescribed CHANTIX.

Outcomes examined in these studies did not include the full range of neuropsychiatric adverse events that have been reported.

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 post-marketing 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 Clinical Trials Experience (6.1)]*. Table 3 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 3. 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 (%)
Mortality (Cardiovascular & All-cause up to 52 wks)		
Cardiovascular death	1 (0.3)	2 (0.6)
All-cause mortality	2 (0.6)	5 (1.4)
Nonfatal Cardiovascular Events (rate on CHANTIX > Placebo)		
Up to 30 days after treatment		
Nonfatal myocardial infarction	4 (1.1)	1 (0.3)
Nonfatal Stroke	2 (0.6)	0 (0)
Beyond 30 days after treatment & up to 52 weeks		
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 4. These events occurred primarily in patients with known cardiovascular disease.

Table 4. 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 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.

5.6 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

5.7 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.

5.8 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)*
- 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)]*
- Angioedema and hypersensitivity reactions *[see Warnings and Precautions (5.6)]*
- Serious skin reactions *[see Warnings and Precautions (5.7)]*

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 5 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 5: 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
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/MEDI AST			
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 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 5, 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, transient ischemic attack, visual field defect.

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 ≥ 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 ≥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 ≥ 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 post-marketing reports of new or worsening seizures in patients treated with CHANTIX *[see Warnings and Precautions (5.2)]*.

There have been post-marketing 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 (5.6)]*.

There have also been reports of serious skin reactions, including Stevens-Johnson Syndrome and erythema multiforme, in patients taking CHANTIX *[see Warnings and Precautions (5.7)]*.

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 studies varenicline was excreted in milk of lactating animals. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from CHANTIX, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

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 yrs) for 7 consecutive days was similar to that of younger subjects. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Varenicline is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function [*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) and 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 1000 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

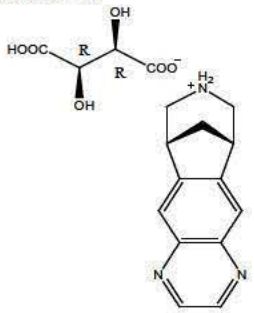
In case of overdose, standard supportive measures should be instituted as required.

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 □ablets contain varenicline (as the tartrate salt), which is a partial agonist selective for $\alpha_4\beta_2$ nicotinic acetylcholine receptor subtypes.

Varenicline, as the tartrate salt, is a powder which is a white to off-white to slightly yellow solid with the following chemical name: 7,8,9,10-tetrahydro-6,10-methano-6*H*-pyrazino[2,3- h][3]benzazepine, (2*R*,3*R*)-2,3-dihydroxybutanedioate (1:1). It is highly soluble in water. Varenicline tartrate has a molecular weight of 361.35 Daltons, and a molecular formula of $C_{13}H_{13}N_3 \cdot C_4H_6O_6$. 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 1mg 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 α4β2 neuronal nicotinic acetylcholine receptors. The efficacy of CHANTIX in smoking cessation is believed to be the result of varenicline's activity at α4β2 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 α4β2 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 α4β2 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 α4β2 receptors than to other common nicotinic receptors (>500-fold α3β4, >3500-fold α7, >20,000-fold α1βγδ), or to non-nicotinic receptors and transporters (>2000-fold). Varenicline also binds with moderate affinity (Ki = 350 nM) to the 5-HT3 receptor.

12.3 Pharmacokinetics

Absorption/Distribution Maximum plasma concentrations of varenicline occur typically within 3-4 hours after oral administration. Following administration of multiple oral doses of varenicline, steady-state conditions were reached within 4 days. Over the recommended dosing range, varenicline exhibits linear pharmacokinetics after single or repeated doses. In a mass balance study, absorption of varenicline was virtually complete after oral administration and systemic availability was ~90%. Oral bioavailability of varenicline is unaffected by food or time-of-day dosing. Plasma protein binding of varenicline is low (≤20%) and independent of both age and renal function.

Metabolism/Elimination The elimination half-life of varenicline is approximately 24 hours. Varenicline undergoes minimal metabolism, with 92% excreted unchanged in the urine. Renal elimination of varenicline is primarily through glomerular filtration along with active tubular secretion possibly via the organic cation transporter, OCT2.

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

Renal Impairment: Varenicline pharmacokinetics were unchanged in subjects with mild renal impairment (estimated creatinine clearance >50 mL/min and ≤80 mL/min). In 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 Cmax 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), and Use in Specific Populations (8.6)]*. Additionally, in subjects with ESRD, varenicline was efficiently removed by hemodialysis *[see Overdosage (10)]*.

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 yrs) for 7 consecutive days was similar to that of younger subjects.

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.

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

Drug-Drug Interactions Drug interaction studies were performed with varenicline and digoxin, warfarin, transdermal nicotine, bupropion, cimetidine, and metformin. No clinically meaningful pharmacokinetic drug-drug interactions have been identified.

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

In vitro studies demonstrated that varenicline does not inhibit human renal transport proteins at therapeutic concentrations. Therefore, drugs that are cleared by renal secretion (e.g., metformin [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., cimeditine [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.

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 exposure based on AUC). Rats were administered varenicline (1, 5, and 15 mg/kg/day) by oral gavage for 2 years. In male rats (n = 65 per sex per dose group), incidences of hibernoma (tumor of the brown fat) were increased at the mid dose (1 tumor, 5 mg/kg/day, 23 times the maximum recommended human daily exposure based on AUC) and maximum dose (2 tumors, 15 mg/kg/day, 67 times the maximum recommended human daily exposure based on AUC). The clinical relevance of this finding to humans has not been established. There was no evidence of carcinogenicity in female rats.

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

Impairment of Fertility There was no evidence of impairment of fertility in either male or female Sprague-Dawley rats administered varenicline succinate up to 15 mg/kg/day (67 and 36 times, respectively, the maximum recommended human daily exposure based on AUC at 1 mg twice daily). However, a decrease in fertility was noted in the offspring of pregnant rats who were administered varenicline succinate at an oral dose of 15 mg/kg/day (36 times the maximum recommended human daily exposure based on AUC at 1 mg twice daily). This decrease in fertility in the offspring of treated female rats was not evident at an oral dose of 3 mg/kg/day (9 times the maximum recommended human daily exposure based on AUC at 1 mg 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 (CO≤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.

Three additional studies were conducted in patients with cardiovascular disease, in patients with chronic obstructive pulmonary disease *[see Clinical Studies (14.4)]*, and in patients instructed to select their quit date within days 8 and 35 of treatment *[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

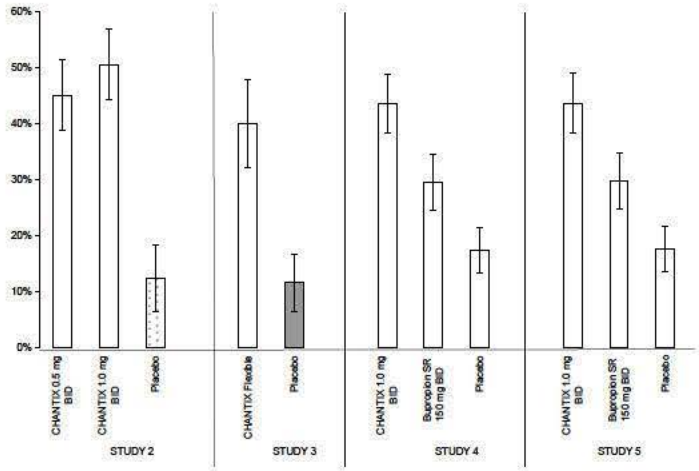


Table 6: Continuous Abstinence, Weeks 9 through 12 (95% confidence interval)

	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 7).

Figure 2: Continuous Abstinence, Weeks 9 through 52

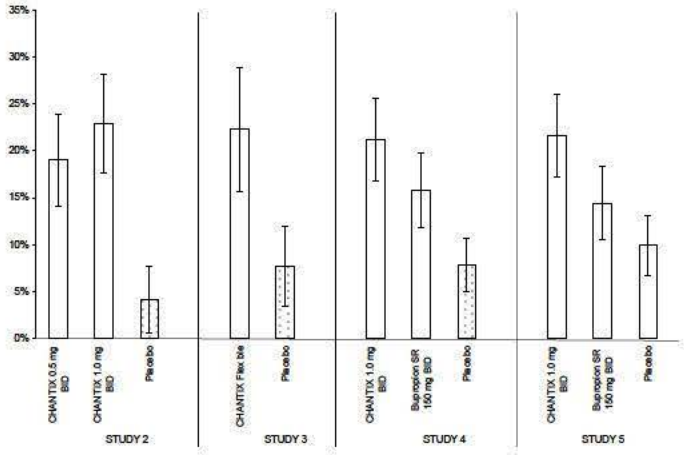


Table 7: Continuous Abstinence, Weeks 9 through 52 (95% confidence interval) across different studies

	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%)

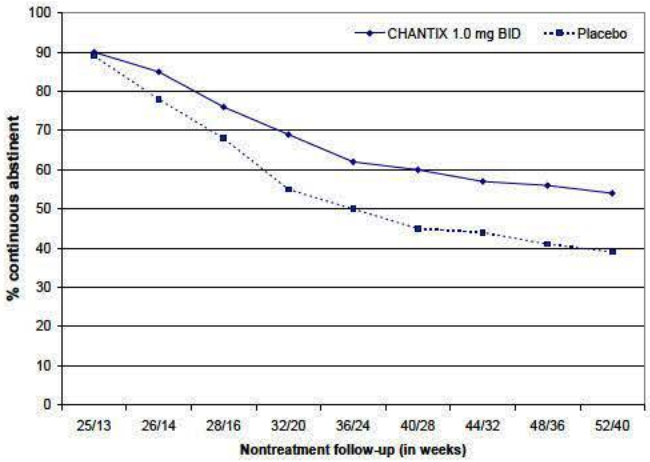
BID = twice daily

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 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 ≥ 35 years with mild-to-moderate COPD with post-bronchodilator FEV1/FVC <70% and FEV1 ≥ 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 8: 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

14.5 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%).

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 Month PAK (First month of therapy): Pack includes 1 card of 0.5 mg x 11 tablets and 3 cards of 1 mg x 14 tablets	NDC 0069-0471-97
	Continuing Month PAK (Continuing months of therapy): Pack includes 4 cards of 1 mg x 14 tablets	NDC 0069-0469-97
	Starting Month Box: 0 5 mg x 11 tablets and 1 mg x 42 tablets	NDC 0069-0471-02
	Continuing Month Box : 1 mg x 56 tablets	NDC 0069-0469-12
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)

17.1 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)]*.

17.2 How To Take

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

17.3 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)]*.

17.4 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)]*.

17.5 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)]*.

17.6 Counseling and Support

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

17.7 Neuropsychiatric Symptoms

Inform patients that some patients have experienced changes in mood (including depression and mania), psychosis, hallucinations, paranoia, delusions, homicidal ideation, aggression, anxiety, and panic, as well as suicidal ideation and suicide when attempting to quit smoking while taking CHANTIX. If patients develop agitation, hostility, depressed mood, or changes in behavior or thinking that are not typical for them, or if patients develop suicidal ideation or behavior, they should be urged to discontinue CHANTIX and report these symptoms to their healthcare provider immediately *[see Boxed Warning, Warnings and Precautions (5.1), Adverse Reactions (6.2)]*.

17.8 History of Psychiatric Illness

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

17.9 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.

17.10 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)]*.

17.11 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)]*.

17.12 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)]*.

17.13 Cardiovascular Events

Patients should be instructed to notify their health care 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), and Adverse Reactions (6.1)]*.

17.14 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 (5.6), and Adverse Reactions (6.2)]*.

17.15 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 (5.7), and Adverse Reactions (6.2)]*.

17.16 Vivid, Unusual, or Strange Dreams

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

17.17 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 *[see Use in Specific Populations (8.1 and 8.3)]*.

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

LAB- 0327-18.X

MEDICATION GUIDE

CHANTIX® (CHANT-iks)

(varenicline) Tablets

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

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

New or worse mental health problems, such as changes in behavior, hostility, agitation, depressed mood, and 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.

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

Stop taking CHANTIX and call your doctor right away if you, your family, or caregiver notice agitation, hostility, depression or changes in your behavior or thinking that are not typical for you, or you develop any of the following symptoms:

- thoughts about suicide or dying, or attempts to commit suicide
- new or worse depression, anxiety, or panic attacks
- feeling very agitated or restless
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- abnormal thoughts or sensations
- seeing or hearing things that are not there (hallucinations)
- feeling people are against you (paranoia)
- feeling confused
- other unusual changes in behavior or mood

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, depressed mood, trouble sleeping, irritability, frustration, anger, feeling anxious, difficulty concentrating, restlessness, decreased heart rate, and increased appetite or 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.

See "What are the possible side effects of CHANTIX?" for more information about other side effects.

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 doctor before taking CHANTIX?

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

Before you take CHANTIX, tell your doctor 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 doctor 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. You and your doctor should decide if you will breastfeed or take CHANTIX. You should not do both.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins and herbal supplements. Your doctor 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 doctor if you use other treatments to quit smoking.

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

How should I take CHANTIX?

- There are 2 ways that you can use CHANTIX to help you quit smoking. Talk to your doctor about the following 2 ways to use

CHANTIX:

Choose a **quit date** when you will stop smoking. Start taking CHANTIX 1 week (7 days) before your **quit date**.

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.

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 doctor.

- 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	• White tablet (0.5 mg) • Take 1 tablet each day
Day 4 to Day 7	• White tablet (0.5 mg) • Take 1 in the morning and 1 in the evening
Day 8 to end of treatment	• Blue 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 doctor 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 doctor if you are having side effects such as nausea, strange dreams, or sleep problems. Your doctor 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:
    - o increased drunkenness (intoxication)
    - o unusual or sometimes aggressive behavior
    - o 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 doctor 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
- **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 doctor about side effects that bother you or that do not go away.

These are not all the side effects of CHANTIX. Ask your doctor 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 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 doctor. You can ask your doctor 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**.

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.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Distributed by

Pfizer Labs

Division of Pfizer Inc, NY, NY 10017

Revised September 2014

LAB-0328-11.X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021928/S-038

REMS

NDA 21-928
Chantix® (Varenicline) Tablets
Nicotinic Receptor Partial Agonist
Aid to Smoking Cessation

Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755
212-733-2323

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL

The goal of this REMS is to inform patients about the potential serious risk of neuropsychiatric adverse events associated with the use of CHANTIX.

II. REMS ELEMENTS

A. Medication Guide

A Medication Guide will be dispensed with each Chantix (varenicline) prescription in accordance with 21 CFR 208.24.

B. Timetable for Submission of Assessments

Pfizer will submit REMS Assessments to FDA 18 months, 3 years, and 7 years following the initial REMS approval of October 19, 2009. To facilitate inclusion of as much information as possible, while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment.

Pfizer Inc will submit each assessment so that it will be received by the FDA on or before the due date.

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/s/

JUDITH A RACOOSIN
09/19/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021928/S-038

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	9/13/14
From	Judith A. Racoosin, MD, MPH
Subject	Seizures, potentiation of interaction with alcohol
NDA # **Supplement#**	21-928 S-032; S-038
Applicant	Pfizer
Date of Submission	S-032: Response to Information Request - 8/14/13 S-032: Labeling Supplement - 10/24/13 S-038: Labeling Supplement – 9/3/2014
Relevant reviews	DPV II review: Seizures – 6/19/14 DAAAP review: Seizures – 7/29/14 DPV II review: Alcohol interaction – 7/21/14 DAAAP review: Alcohol interaction – 7/30/14 DRISK review: REMS modification – 9/17/14 PLT review: REMS modification – 7/17/14, 9/18/14
Proprietary Name / Established (USAN) names	CHANTIX (varenicline tartrate) tablet, film coated
Dosage forms / Strength	Oral Tablet
Indication(s)	Aid to smoking cessation treatment (approved)

Introduction

Chantix (varenicline tartrate, NDA 21928, Pfizer) is a partial agonist at the α4β2 nicotinic receptor that was approved in May 2006 as an aid to smoking cessation. The α4β2 nicotinic receptor has been shown to be responsible for the reinforcing properties of nicotine in animal models.

Drug Interaction between varenicline and alcohol

In May 2013, because of concerns raised by spontaneous adverse event reports and an inquiry from external stakeholders, DAAAP asked Pfizer to search their database for any cases that indicated the potential for varenicline to reduce tolerance to alcohol. A response to the information request was submitted in August 2013, followed by a labeling supplement (S-032) in October 2013, in which Pfizer proposed the following statement for the Drug Interactions section of labeling:

(b) (4)

DAAAP consulted the Division of Pharmacovigilance II (DPV II) to review the FDA Adverse Event Reporting System (FAERS) for cases reporting symptomatology related to concomitant use of varenicline and alcohol.

In Dr. Winchell's review of Pfizer's submission and the DPV II review, she concludes the following:

In summary, Pfizer identified several dozen cases in which patients reported increased effects of alcohol while taking Chantix, sometimes associated with bizarre behavior and sometimes limited simply to feeling very intoxicated. Many reported amnesia. Cases of de-challenge and positive re-challenge were reported. This is consistent with some animal findings showing varenicline may increase aversive and sedating effects of alcohol. Most cases did not lead to serious outcomes, but cases of self-directed harm, property damage, other-directed violence, arrest, and incarceration were reported. Additionally, decreased alcohol tolerance has the potential for serious outcomes, such as when a patient drives after drinking and does not anticipate the increased level of intoxication.

(b) (4)

section 5.1, Neuropsychiatric symptoms and suicidality. However, our reviews (DAAAP and DPV II) indicate that there are two distinct types of cases. One group describes a potentiation of the intoxicating effect of alcohol, and the other group describes neuropsychiatric events temporally associated with alcohol use. The former group is not currently adequately warned about in varenicline labeling.
The evidence supporting an effect of varenicline on alcohol tolerance is sufficient to warrant inclusion in the Warnings and Precautions section of labeling so that patients will be aware of this risk.

Additionally, new language should be added to Section 5.1 describing the possibility that alcohol may have played a role in potentiating neuropsychiatric events in some cases.

Seizures associated with varenicline use

Since its approval on May 10, 2006, the U.S. package insert for varenicline has listed convulsion (also referred to herein as "seizure") as a rare event in the Nervous System Disorders subsection of the Adverse Reactions section, but the number of seizures observed pre-marketing was too low to draw conclusions about varenicline's potential causal role. Pfizer has reviewed seizures as a safety issue in each Periodic Safety Update Report and has concluded to date that no new labeling was warranted. However, in 2013, both Health Canada and the European Medicines Agency made changes to labeling for Chantix (marketed as Champix outside the US), noting postmarketing reports of seizures and, in the case of the EMA-approved labeling, recommending that the product be used cautiously in patients with a history of seizure.

DAAAP requested that DPV perform a comprehensive review of the potential for Chantix to increase the risk of seizures. DPV performed an analysis of cases in FAERS and the published medical literature; the Division of Epidemiology II (DPV II) evaluated a sponsor-submitted observational study of seizures associated with prescriptions for varenicline; and the Predictive Safety Team in the Office of Clinical Pharmacology assessed the biological plausibility of varenicline-induced seizures.

The executive summary of the joint DPV II/ DEPI II/ PST review follows below:

> This integrated review assesses the risk of seizures in patients using Chantix (varenicline). It was requested by the Division of Anesthesia, Analgesia and Addiction Products (DAAAP), and is

based on analyses completed by the Division of Pharmacovigilance II (DPV-II), the Division of Epidemiology II (DEPI-II), and the Predictive Safety Team (PST). DPV-II's work consisted of an analysis of cases in FAERS1 and the published medical literature. DEPI-II evaluated a sponsor-submitted observational study of seizures associated with prescriptions for varenicline, and the Predictive Safety Team (PST) assessed the biological plausibility of varenicline-induced seizures.

DPV-II identified 64 seizure cases in which the role of varenicline cannot be excluded. The cases include one compelling report from the published medical literature. These 63 cases have been divided into two groups: those clearly designating no history of seizure (n=36; 10 of which had no other contributing factors besides varenicline) and those designating a history of 'controlled seizure' (n=27). The median event onset time from the start of varenicline was 2-3 weeks. Other factors in addition to varenicline that may have contributed to the seizures included co-medications (e.g., antiepileptic and psychiatric) that include seizures as adverse events in the product labeling.

DEPI-II reviewed the sponsor's observational, retrospective claims study. This study concluded that varenicline did not increase the risk of seizure. However, DEPI-II concludes that the study contained significant biases limiting its value in assessing the risk of seizures in patients using varenicline.

The PST, based upon animal data, concluded that it is plausible that varenicline can induce seizures. Varenicline has agonistic activity on several nicotinic receptor subtypes. In animals, stimulation of these receptors by other (non-varenicline) agonists have been reported to cause seizures. Animals devoid of some of these receptors are resistant to nicotine-induced seizures.

In light of the fact that (1) there are numerous compelling cases describing seizure in varenicline users, and (2), there is biological plausibility, we recommend that the varenicline labeling be modified to include a Warning about this adverse reaction.

Issuance of FDAAA Safety Labeling Change Notification Letter

Based on the reviews conducted by DAAAP, DPV II, DEPI II, and PST described above, the review team concluded that there was "new safety information" supporting the need to add warnings to the varenicline product labeling about 1) the risk of a drug interaction with alcohol that may result in the potentiation of intoxication from alcohol, and 2) the occurrence of seizures in association with varenicline use. On August 6, 2014, the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) issued a FDAAA Safety Labeling Change (SLC) notification letter to Pfizer to alert them to add these two new warnings to product labeling, along with the specific labeling text.

Pfizer submitted a response to the FDAAA SLC letter on September 3, 2014 as Supplement 038. This memorandum reviews Pfizer's counterproposal submitted in S-038.

REMS modification in S-032

S-032, which included the Pfizer-proposed language for the Drug Interactions section, also included a REMS modification which was requested of the sponsor by DAAAP in a REMS modification notification letter dated September 4, 2013. The purposed of the REMS modification was to revise key sections of the Medication Guide to "facilitate the goal of informing patients about neuropsychiatric events with Chantix… so as to furnish adequate information for the safe and effective use of the drug."

In addition to reviewing Pfizer's response to the FDAAA SLC, this memo summarizes the findings of the reviews conducted by the Division of Risk Management (DRISK) and the Patient Labeling Team (PLT)/Office of Prescription Drug Promotion (OPDP) of Pfizer's REMS modification that was submitted as part of S-032, and resubmitted along with S-038.

Pfizer's response to the FDAAA SLC notification letter[1]

On September 3, 2014, Pfizer submitted their response to the FDAAA SLC notification letter. It was not a rebuttal, but substantial revisions to FDA's labeling language were proposed. No data was submitted to support the labeling revisions.

Varenicline-alcohol interaction

FDA language to be added to section 5.1: Neuropsychiatric Symptoms and Suicidality

> Some reported neuropsychiatric events, including self- and other-directed aggression, may have been potentiated by concomitant use of alcohol. [see *Potentiation of Effects of Alcohol* (5.6)]

Pfizer counterproposal:

FDA addition of new section 5.3: Potentiation of Intoxicating Effects of Alcohol

> There have been post-marketing reports of patients experiencing increased intoxicating effects of alcohol while taking Chantix. Some cases described bizarre and sometimes aggressive

[1] Only the changes to the WARNINGS and PRECAUTIONS section are summarized here. There are related revisions in Highlights, Adverse Reactions, and Patient Counseling Information that convey the changes being required in the WARNINGS and PRECAUTIONS section.

behavior, and were often accompanied by amnesia for the events. Advise patients to use caution when consuming alcohol while taking Chantix until they know how Chantix may affect their tolerance for alcohol.

Pfizer counterproposal:

5.3 (b) (4) Alcohol

There have been post-marketing reports of patients experiencing increased intoxicating effects of alcohol while taking (b) (4) CHANTIX. Some cases described unusual (b) (4) and sometimes aggressive behavior, and (b) (4) were (b) (4) accompanied by amnesia- (b) (4) [see Adverse Reactions (6.2)] (b) (4)

(b) (4)

FDA comment:

(b) (4)

The DPV II review used a rigorous case definition to identify cases of decreased alcohol tolerance which required a statement in the case narrative that suggested that prior to varenicline treatment the patient was able to tolerate the amount of alcohol that in the case report resulted in the patient becoming excessively intoxicated. Consistent with that, Dr. Winchell found that the postmarketing cases in the Pfizer submission, "... provide multiple examples of exaggerated and uncharacteristic response to alcohol including at least eight cases of violent behavior involving consumption of small amounts of alcohol."

(b) (4) . Both DPV II and DAAAP found case reports that strongly suggest that varenicline potentiates the intoxicating effect of alcohol, and may have played a role in potentiating some of the neuropsychiatric events that were reported in association with varenicline use.

In a teleconference held September 16, 2014, the FDA review team and Pfizer discussed their September 3, 2014 labeling proposal. Agreement was reached regarding renaming the 5.3 section with the title "Interaction with Alcohol". This name is in keeping with other subsections of the Warnings and

Precautions that indicate what the warning is about (e.g., Accidental Injury), but doesn't include in the subsection title the actual effect. Most of the language reverted back to FDA's original proposal except for the replacement of [redacted] (b) (4) [redacted]. Finally, FDA made the decision to specifically state that patients should be advised to reduce their alcohol consumption until they know whether varenicline affects their tolerance [redacted] (b) (4)

Regarding the statement in 5.1, [redacted] (b) (4) "worsened". Otherwise the modification just reflects some reorganization for clarity.

Finally, [redacted] (b) (4) [redacted]

Final agreed upon language:

5.1 (added to) Neuropsychiatric Symptoms and Suicidality

Some reported neuropsychiatric events, including unusual and sometimes aggressive behavior directed to oneself or others, may have been worsened by concomitant use of alcohol [see Interaction with Alcohol (5.3), Adverse Reactions (6.2)].

5.3 Interaction with Alcohol

There have been post-marketing 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) [redacted] (b) (4)

Seizure

FDA addition of new section:

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 conditions that can lower the seizure threshold. Advise patients to discontinue Chantix and not restart it if they experience a seizure while on treatment.

Pfizer counterproposal:

5.2 Seizures

(b) (4)

[redacted]

FDA comment:

Pfizer's counterproposal serves to (b) (4) [redacted] The regulations describing the criteria for the Warnings and Precautions section of product labeling states that this section "must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established."[2] (b) (4) [redacted]

In a teleconference held September 16, 2014, the FDA review team and Pfizer discussed their September 3, 2014 labeling proposal. Based on the discussion, Pfizer agreed to revert back to FDA's original proposal with the exception of one point. Pfizer took issue with the advice to not restart Chantix if they experience a seizure while taking it. They pointed out that if a patient turned out to have a specific identified cause for their seizure that was unrelated to Chantix, their healthcare provider may want to consider restarting it. FDA agreed to remove that advice, instead adding language about the patient contacting a healthcare provider immediately should they have a seizure.

[2] See 21 CFR 201.57(c)(6)

Final agreed upon language:

> 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)].

REMS modification

DRISK review

In a review dated September 17, 2014, DRISK reviewer Cathy Miller summarized the regulatory history leading to the REMS modification and provided the rationale for requesting the revisions to the MedGuide and the REMS goal as follows:

- Revisions to the MedGuide to address poor understanding of serious allergic reactions, serious skin reactions, and CV risk associated with Chantix by updating the "What is the most important information I should know about Chantix?" section of the MedGuide, while improving other sections of the MedGuide to be consistent with the language in the approved labeling (communicated to the Sponsor in DAAAP's September 4, 2013 Prior Approval Supplement Request/REMS Modification Notification letter)

- Revision to the REMS document to focus the REMS goal on the primary risk for Chantix REMS as 'potential (b) (4) adverse events' along with revisions to the REMS Assessment Plan to focus only on patient knowledge of the neuropsychiatric risks (communicated by DAAAP to the Sponsor via email on October 30, 2013).

DRISK endorsed the revised REMS goal as proposed by Pfizer in their November 8, 2013 submission and resubmitted in their September 3, 2014 submission:

> - The goal of this REMS is to inform patients about the (b) (4) ~~e~~ potential (b) (4) serious risk of neuropsychiatric adverse events associated with the use of Chantix.

Regarding the revisions to the MedGuide revisions, the DRISK review notes that the "proposed revisions to the Chantix MG were previously reviewed by the PLT in their review dated February 15, 2013 with revisions based on the REMS 3-year assessment findings ... The PLT also conducted a Patient Labeling Review July 17, 2014 with recommended revisions to the MG for Supplement S- (b) (4) based on data submitted in the supplement pertaining to Chantix and alcohol, along with added safety information about seizures with Chantix use. The MG is currently under an additional review by the PLT under

separate cover based on the September 3, 2014 Sponsor submission of PAS/REMS Modification (S-038) response to the Agency's SLC issued August 6, 2014."

PLT/OPDP review

The joint PLT/OPDP review dated July 17, 2014 proposes revisions to the MedGuide to incorporate patient-friendly information about the varenicline-alcohol interaction resulting in the potentiation of the intoxicating effect of alcohol and the risk of seizures in patients taking varenicline.

The revisions also address earlier issues including rewording of information describing the risk of allergic reactions and clarification of information about who should not take varenicline, and what the patient should tell the healthcare provider before taking varenicline.

In a review dated September 18, 2014, PLT and OPDP issued a joint review of the MedGuide language agreed upon in the teleconference with Pfizer on September 16, 2014. They concluded, "We find the Applicant's proposed MG acceptable as revised with the agreed upon changes between the review team and Pfizer, Inc. during the teleconference dated September 16, 2014, and as submitted on September 17, 2014."

Conclusions/Next steps

The labeling language agreed upon by FDA and Pfizer for the package insert and the Medication Guide during the September 16, 2014 teleconference and reflected in their labeling submission on September 17, 2014 regarding the FDAAA safety labeling changes should be approved.

DAAAP agrees with the DRISK and PLT/OPDP recommendations regarding revisions to the REMS goal and the MedGuide text.

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/s/

JUDITH A RACOOSIN
09/18/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021928/S-038

OTHER REVIEW(S)

Division of Anesthesia, Analgesia, and Addiction Products

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: NDA 21928/ S-032, S-036, & S-038
Name of Drug: Chantix (varenicline) Tablets; 0.5 mg and 1 mg
Applicant: Pfizer, Inc.

Labeling Reviewed

Submission and Receipt Date: S-032: October 24, 2013
S-036: April 8, 2014
S-038: September 3, 2014

Background and Summary Description:

Supplement S-032 proposes revisions to the **DRUG INTERACTIONS** section of the Package Insert regarding a potential interaction between alcohol and varenicline and includes a proposed modification to the approved risk evaluation and mitigation strategy (REMS), including revisions to the Medication Guide and revisions to the Chantix REMS goal.

Supplement S-036 proposes changes to the Package Insert based on meta-analyses of varenicline clinical trials and published observational studies pertaining to serious neuropsychiatric events.

Supplemental S-038 proposes revisions to the labeling for Chantix. The agreed upon changes to the language included in our August 6, 2014, letter are included in the appended labeling text. S-038 also includes additional proposed modifications to the approved risk evaluation and mitigation strategy (REMS), comprising further revisions to the Medication Guide as well as revisions to the Chantix REMS goal.

Review

The revised labeling submitted under S-032, S036, and S-038 was compared to labeling approved on February 19, 2013, for S-030.

Please note that the Sponsor's proposed omissions are indicated by strikeovers, inclusions by underlined text. See the attached revised label.

Recommendations

These supplements are recommended for approval.

Ayanna Augustus, Ph.D., RAC	September 18, 2014
Regulatory Project Manager	Date
Parinda Jani	September 18, 2014
Chief, Project Management Staff	Date

16 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

AYANNA S AUGUSTUS
09/18/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021928/S-038

RISK MITIGATION and RISK ASSESSMENT REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

REMS MODIFICATION REVIEW

Date:	September 17, 2014
Reviewer(s)	Cathy A. Miller, M.P.H., B.S.N., Risk Management Analyst Division of Risk Management (DRISK)
Team Leader	Kimberly Lehrfeld, Pharm.D., Team Leader, DRISK
Acting Deputy Director:	Reema Mehta, Pharm.D., M.P.H., Acting Deputy Director, DRISK
Drug Name(s):	Chantix (varenicline) Tablets
Therapeutic class:	Smoking Cessation Agent
Dosage and Route:	0.5 mg and 1 mg Oral tablets
OND Review Division	Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Application Type/Number:	NDA 021928
Supplement # and Date Received	S-032 received October 24, 2013 (Seq. No. 0307); amended November 8, 2013 (Seq. No. 208) S-038 received September 3, 2014 (Seq. No. 0332)
PDUFA/Action Date	N/A
Applicant/sponsor:	Pfizer, Inc.
OSE RCM #:	2013-2680
TSI #:	1134

n/a = not applicable

1. INTRODUCTION

The purpose of this review is to document the Division of Risk Management's (DRISK) evaluation of the proposed modifications to the risk evaluation and mitigation strategy (REMS) for Chantix (varenicline) tablets, NDA 21928. The proposed modifications to the REMS were submitted by Pfizer on October 24, 2013, and amended November 4, 2013 as part of a Prior Approval Supplement (PAS) (S-032), and resubmitted again in a new PAS (S-038), in response to the Agency's Safety Labeling Change (SLC) Notification to Pfizer on September 4, 2014.

The modification submitted on October 24, 2013 proposed revisions to the Medication Guide (MG) to improve patient knowledge about the risks associated with Chantix, specifically, cardiovascular (CV) events, allergic reactions and skin reactions. An amendment to the PAS submitted November 8, 2013, included revisions to the REMS goal to refine the goal to focus only on neuropsychiatric risks.

1.1. BACKGROUND

Chantix (varenicline) is a high-affinity selective partial agonist of the α4β2 nicotinic receptor. The α4β2 nicotinic receptor has been shown to be responsible for the reinforcing properties of nicotine in animal models. Based on the activity at the nicotinic receptor, varenicline could be expected to mitigate withdrawal symptoms and reduce the reinforcing effects of nicotine, leading to efficacy in helping smokers stop smoking.

Chantix is available in 0.5 mg and 1 mg capsules. Chantix dosing should begin one week before the date set by the patient to stop smoking or alternatively, the patient can begin dosing, and then quit smoking between days 8 and 35 of treatment. The starting week dose is 0.5 mg once daily on days 1-3 and 0.5 mg twice daily on days 4-7. Continuing weeks dosing is 1 mg twice daily for a total of 12 weeks. An additional 12 weeks of treatment is recommended for successful quitters to increase likelihood of long-term abstinence.

Chantix was originally approved on May 10, 2006 and is indicated as an aid to smoking cessation treatment. On May 16, 2008, in addition to the approval of a MG for Chantix, the Agency communicated to the Sponsor that under Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA), a REMS should be submitted. The Agency cited that "since Chantix was approved on May 10, 2006, as an aid to smoking cessation treatment, we have become aware of post-marketing reports of neuropsychiatric symptoms, including changes in behavior, agitation, depressed mood, and suicidal thoughts or actions associated with Chantix. This information was not available when Chantix was granted marketing authorization as an aid to smoking cessation treatment. Therefore, we consider this information to be "new safety information" as defined in FDAAA."

The Chantix REMS was approved on October 19, 2009. The goal of the REMS is (b) (4) [redacted]. The REMS elements include a MG and a timetable for submission of assessments (18 months, 3- and 7-years after approval). The Chantix REMS was modified on April 22, 2010, which included revisions to the MG "Who should not take Chantix" section, and

July 22, 2011, also with revisions to the MG to include new information about how to take Chantix and possible side effects. The currently approved version of the REMS is dated July 22, 2011.

1.2. REGULATORY HISTORY

The following is an overview of the regulatory history for Supplement 0032 and 0038:

October 17, 2012: The Sponsor submitted their Chantix 3-year REMS Assessment Report.

December 7, 2012: The Chantix 50-Day meeting was held including the Division of Anesthesia, Analgesia and Addiction Products (DAAAP), DRISK, Office of Medical Policy/Patient Labeling Team (PLT), and the Office of Compliance (OC). Discussion focused on the Chantix 3-Year REMS assessment findings. The team concluded that the survey results demonstrated that patients maintained a high level of understanding of the neuropsychiatric risks of Chantix use. This finding is consistent with the prior REMS Assessment Report. However, the survey found that there was a low understanding of the serious risks of CV events, serious allergic and skin reactions specifically the "What is the most important information I should know about Chantix?" section. The team recommended revising the MG to address these findings and to align other areas of the MG to be consistent with the approved labeling.

February 15, 2013: PLT completed their review of the Chantix MG.[1]

February 28, 2013: DRISK recommended a REMS Modification Letter be sent to the Sponsor for revisions to the MG.[2]

May 10, 2013: In conjunction with discussions about findings of the 3-Year REMS Assessment[3] between DAAAP and DRISK, revisions to the REMS goals to "focus only on neuropsychiatric risks" were recommended.

May 24, 2013: Based on postmarketing reports, DAAAP sent an email communication information request[4] to the Sponsor asking for additional information about Chantix and alcohol ingestion.

September 4, 2013: DAAAP sent a PAS Request/REMS Modification Notification Letter to the Sponsor with recommended revisions to the MG based on the PLT recommendations, dated February 15, 2013.

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[1] Mills, S. DMMP/PLT Patient Labeling Review of Medication Guide DMPP/Patient Labeling Review of Medication Guide (MG) for Chantix (varenicline) dated February 15, 2013.

[2] Smith, D. DRISK REMS Modification Memorandum for Chantix (varenicline) dated February 28, 2013.

[3] Auth, D.DRISK Addendum review of 3-Year Assessment report for Chantix (varenicline) dated May 10, 2013.

[4] Won, L. DAAAP Information Request email communication to Pfizer for Chantix (varenicline) sent May 24, 2013.

October 24, 2013: In response to the September 4, 2013 REMS Modification Notification Letter, the Sponsor submitted a PAS (S-032)/Proposed REMS modification. They proposed the following modifications:

- MG Revisions Based on 3-Year REMS Assessment and PLT Review: The revised MG reflected the Agency recommended revisions.
- Chantix and Alcohol Use Data: Although not requested in the REMS Modification Notification Letter, the Sponsor submitted data pertaining to concomitant use of Chantix and alcohol, based on DAAAP's Information Request email dated May 24, 2013. In addition, the Sponsor submitted revisions to reflect the information in the Drug Interactions section of the prescribing information (PI) and the MG.

October 30, 2013: DAAAP communicated via email to the Sponsor, "OSE and DAAAP have determined that the goal of the Chantix (varenicline) REMS is too broad and should be modified to focus on the risk of neuropsychiatric adverse events in patients taking Chantix. We would like the Chantix REMS goal to be modified to below:

- The goal of this REMS is to inform patients about the serious risks of neuropsychiatric adverse events associated with the use of CHANTIX. ~~including the potential risk of serious neuropsychiatric symptoms in patients taking CHANTIX.~~

November 8, 2013: Sponsor submitted an amendment to S-032, to revise the Chantix REMS goal as follows:

- The goal of this REMS is to inform patients about the ~~serious risks associated with the use of Chantix, including the~~ potential ~~risk of~~ serious risk of neuropsychiatric adverse events associated with the use of Chantix.

April 23, 2014: Based on DAAAP's preliminary evaluation of the Sponsor's data pertaining to concomitant use of Chantix and alcohol submitted in S-032, DAAAP requested more detailed information via email about select Chantix and alcohol interaction cases. Specifically, DAAAP requested the following: *"Provide the full information (e.g. the verbatim report and any other information collected) about the 34 cases of patients who "experienced a decreased tolerance/exaggerated response to alcohol, about which we were told "Among the 22 cases reporting information on the quantity of alcohol consumed, in 19 instances, the patient had consumed 4 drinks or less. There were 4 cases reporting on patients who had consumed more than 4 drinks, ranging from 1 bottle of wine to 12 cans for beer. The 34 cases in this dataset were descriptions of patients who reportedly had a reduced tolerance to alcohol, got drunk more easily or got drunk from consuming a relatively small quantity of alcohol. Memory loss and/or black outs were described in 10 of these 34 cases."*[5]

April 30, 2014: The Sponsor submitted additional data pertaining to concomitant use of Chantix and alcohol cases.

[5] Augustus, A. DAAAP Email communication information request to Pfizer for Chantix (varenicline) Supplement S-032 sent April 23, 2014.

July 17, 2014: The PLT completed their review of the Chantix MG for supplement S-032 based on data submitted in the supplement pertaining to Chantix and alcohol, along with added safety information about seizures with Chantix use.

August 6, 2014: Based on DAAAP's evaluation of data pertaining to concomitant use of Chantix and alcohol, DAAAP sent a SLC Notification/REMS Modification Notification[6] to the Sponsor. The letter included DAAAP's revised PI and MG that reflect changes associated with Chantix and alcohol, along with added information about Chantix use and seizures, based on postmarketing reports of seizures with Chantix use. We note that this correspondence included the revised MG which was previously reviewed by PLT for supplement S-032.[7]

September 3, 2014: The Sponsor submitted PAS/Proposed REMS Modification as a new supplement (S-038). Supplement 38 included all changes to the PI, MG and REMS document that were originally included in S-32 as well as new language related to Chantix use with alcohol requested in the SLC Notification/REMS Modification Notification Letter. The following revised materials were submitted:

- Revised PI to incorporate required SLCs pertaining to Chantix and alcohol use and additional safety information pertaining to reports of seizures in patients using Chantix.
- Revised MG to incorporate required SLCs pertaining to Chantix and alcohol use, additional safety information pertaining to reports of seizures in patients using Chantix and revisions to better communicate the risks of CV events, serious allergic and skin reactions.
- Revised REMS document reflecting the originally requested modification to the Chantix REMS goal statement as previously submitted in supplement S-032 amendment dated November 8, 2013 to read: The goal of this REMS is to inform patients about the ~~serious risks associated with the use of Chantix, including the~~ potential ~~risk of~~ serious <u>risk of</u> neuropsychiatric <u>adverse events associated with the use of</u> Chantix, which is the focus of this review.

September 5, 2014: Based on pending SLC actions as indicated above, DRISK sent an email communication to DAAAP querying about whether the risks of seizures rise to the level of needing additional risk management considerations beyond labeling. In their response the same date, DAAAP indicated that they would not recommend a REMS to address the risk of seizure for this product.

2. MATERIALS REVIEWED

2.1. SUBMISSIONS

The following submissions, listed by date received, were reviewed from NDA 21928 for the proposed Chantix REMS Modification:

[6] Rappaport, B. DAAAP Safety Labeling Change Notification/REMS Modification Notification for Chantix (varenicline) to Pfizer sent August 6, 2014.

[7] Mills,S. PLT Patient Labeling Review of the MG for Chantix (varenicline) dated July 17, 2014.

- Pfizer Prior Approval Labeling Supplement/Proposed REMS Modification for Chantix (varenicline) received October 24, 2013 (Supplement S-032/Seq. No. 307)
    - Pfizer Prior Approval Labeling Supplement/Proposed REMS Modification Amendment for Chantix (varenicline) received November 8, 2013 (Supplement S-032/Seq. No. 308)
- Pfizer Safety Labeling Changes Under 505(o)(4)-Prior Approval Labeling/Proposed REMS Modification for Chantix (varenicline) received September 3, 2014 (Supplement S-038/0332)

2.2. OTHER MATERIALS INFORMING OUR REVIEW

- DAAAP Prior Approval Supplement Request REMS Modification Notification for Chantix (varenicline) dated September 4, 2013
- Mills, S. Patient Labeling Review of the Medication Guide for Chantix (varenicline) (Supplement S-011) dated February 15, 2013
- Mills, S. Patient Labeling Review of the Medication Guide for Chantix (varenicline) (Supplement S-032) dated July 17, 2014.
- Auth, D. DRISK REMS Assessment Review for Chantix (varenicline) dated May 10, 2013

3. RATIONALE FOR PROPOSED REMS MODIFICATIONS

On October 17, 2012, the Chantix REMS 3-year Assessment Report[8] was submitted to the Agency for review. The survey results of the report indicated that patients had a high level of understanding of the neuropsychiatric risks of Chantix use. However the survey found that there was a lower patient understanding CV events, serious allergic reactions and serious skin reactions associated with Chantix use.

The DRISK 3-Year Chantix REMS Assessment Review[9] included preliminary discussions about the findings at the 50-Day meeting on December 7, 2012. The findings were that "Recognizing that the primary goal for Chantix REMS is to inform patients the risk of serious neuropsychiatric adverse reactions, we consider the REMS goal is met. However, there is room for improvement in the understanding rates for the serious neuropsychiatric risks. Furthermore, the understanding rates for other risks (serious allergic reactions, serious skin reactions, and CV risk) relatively low. Therefore, we recommend considering revisions to the REMS materials." These discussions prompted subsequent proposals to revise the MG to improve understanding of serious allergic reactions, skin reactions and CV risks.

[8] Pfizer REMS 3-Year Assessment Survey Report for Chantix (varenicline) received 10/17/2012 (Supplement S-011/Seq. No. 296).

[9] Ju. J. DRISK Chantix -3-Year Assessment Report Review for Chantix (varenicline) dated December 20, 2012.

Discussions between DRISK and DAAAP continued after the Assessment review was completed which focused on the Chantix REMS goal statement. The REMS goal, as currently written is "to inform patients about the serious risks associated with the use of Chantix, including the potential risk of serious neuropsychiatric symptoms in patients taking Chantix." Since the REMS was prompted by post-marketing reports of neuropsychiatric symptoms, as stated in both the Chantix REMS Notification Letter (May 16, 2008) and the Chantix REMS Approval Letter (October 19, 2009), there was agreement that the intended goal of the Chantix REMS Program, is "to inform patients about the serious risk of neuropsychiatric events", rather than informing patients about all of the risks associated with the use of Chantix.

Based on the REMS Assessment findings and goal of the REMS program, DAAAP and DRISK agreed that a REMS modification is necessary including the following revisions:

- Revisions to the MG to address poor understanding of serious allergic reactions, serious skin reactions, and CV risk associated with Chantix by updating the "What is the most important information I should know about Chantix?" section of the MG, while improving other sections of the MG to be consistent with the language in the PI.
- Revision to the REMS document to focus the REMS goal on the primary risk for Chantix REMS as 'potential for psychiatric adverse events' along with revisions to the REMS Assessment Plan to focus only on patient knowledge of the neuropsychiatric risks.

As cited above in Section 1.2 Regulatory History, additional modifications to the Chantix PI and MG were prompted by DAAAP's evaluation of Chantix and alcohol interaction data submitted in supplement (S-032), prompting the SLC for Chantix sent to the Sponsor on August 6, 2014, and a subsequent REMS modification in conjunction with the SLC. The Sponsor's submission incorporated requested information, in addition to their resubmission of the originally requested revision to the REMS goal statement to focus more narrowly on neuropsychiatric events only. The MG will be reviewed under separate cover by the PLT.

Due to administrative processes related to the original prior approval supplement/REMS Modification (S-032) and associated SLC, the Sponsor's resubmission created an additional PAS/REMS Modification (S-038). DAAAPs intention is to take action on both Supplement 32 and 38 at the same time.

4. PROPOSED REMS MODIFICATIONS

4.1. REMS GOALS

The Chantix REMS goals have been revised to focus only on the intended Chantix goal of neuropsychiatric risks. The REMS goal language is revised as follows:

- The goal of this REMS is to inform patients about the ~~serious risks associated with the use of Chantix, including the~~ potential ~~risk of~~ serious <u>risk of</u> neuropsychiatric <u>adverse events associated with the use of</u> Chantix.

4.2. REMS ELEMENTS

4.2.1. MEDICATION GUIDE

The proposed revisions to the Chantix MG were previously reviewed by the PLT in their review dated February 15, 2013 with revisions based on the REMS 3-year assessment findings discussed above in Section 1.2 Regulatory History. The PLT also conducted a Patient Labeling Review July 17, 2014 with recommended revisions to the MG for Supplement S-032[10] based on data submitted in the supplement pertaining to Chantix and alcohol, along with added safety information about seizures with Chantix use. The MG is currently under an additional review by the PLT under separate cover based on the September 3, 2014 Sponsor submission of PAS/REMS Modification (S-038) response to the Agency's SLC issued August 6, 2014.

5. DISCUSSION AND CONCLUSION

Proposed modifications to the Chantix REMS submitted in supplement (S-032) and (S-038) include:

- Revisions to the MG reflecting added safety information pertaining to Chantix use and alcohol, along with additional safety information about seizures associated with Chantix use and revisions to better communicate the risks of CV events, serious allergic and skin reactions.
- Revision of the Chantix REMS goal statement as requested, to more narrowly focus on neuropsychiatric events, which is the primary focus of the program. The goal statement is revised to read "The goal of this REMS is to inform patients about the ~~serious risks associated with the use of Chantix, including the~~ potential ~~risk of~~ serious risk of neuropsychiatric adverse events associated with the use of Chantix, which is the focus of this review."

Changes to the MG are reviewed under separate cover by the PLT. DRISK notes that as part of our safety evaluation for the proposed modifications, we consulted with DAAAP regarding the added safety information pertaining to seizures and Chantix use. In email communications between DRISK and DAAAP on September 5, 2014[11] concerning the added seizure information for Chantix, DRISK queried DAAAP about whether this information rises to the level of additional risk management considerations beyond the recommended labeling revisions outlined in the SLC. DAAAP replied that they did not recommend a REMS to address the risks of seizures associated with use of Chantix. DRISK concurs with this evaluation.

DRISK finds the Sponsor's REMS modification for Chantix (varenicline tablets) which proposes a revision to the Chantix REMS goal, submitted on November 8, 2013, to be acceptable. The REMS document, appended to this review, was revised to be consistent

[10] Mills, S. PLT Patient Labeling Review of Medication Guide for Chantix (varenicline) for Supplement (S-032 dated July 17, 2014

[11] Miller, C. (DRISK) and Winchell, C. (DAAAP) Email communications regarding Chantix (varenicline) use and seizure activity dated September 5, 2014.

with the agreed upon Chantix REMS Program goal to focus specifically on neuropsychiatric risks.

6. RECOMMENDATIONS

The OSE, DRISK recommends approval of the proposed REMS modification for revision to the Chantix REMS Goal, originally submitted in prior approval supplement/REMS Modification Amendment dated November 8, 2013 for supplement (S-032), and resubmitted as a prior approval supplement/REMS Modification on September 3, 2014 for supplement (S-038).

APPENDED INFORMATION

Appendix 1: REMS document

NDA 21-928
Chantix® (Varenicline) Tablets
Nicotinic Receptor Partial Agonist
Aid to Smoking Cessation

Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755
212-733-2323

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL

The goal of this REMS is to inform patients about the potential serious risk of neuropsychiatric adverse events associated with the use of CHANTIX.

II. REMS ELEMENTS

A. Medication Guide

A Medication Guide will be dispensed with each Chantix (varenicline) prescription in accordance with 21 CFR 208.24.

B. Timetable for Submission of Assessments

Pfizer will submit REMS Assessments to FDA 18 months, 3 years, and 7 years following the initial REMS approval of October 19, 2009. To facilitate inclusion of as much information as possible, while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment.

Pfizer Inc will submit each assessment so that it will be received by the FDA on or before the due date.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CATHY A MILLER
09/17/2014

REEMA J MEHTA
09/17/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021928/S-038

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

From:	Augustus, Ayanna
To:	Donohew, Lilya
Cc:	Augustus, Ayanna
Subject:	RE: Chantix draft S-036 and S-038 labels
Date:	Wednesday, September 17, 2014 11:55:52 AM
Attachments:	CHANTIX_S-038_9_16_14_DRAFT_as per tcon_jar.doc CHANTIX_S-036_9_16_14 DRAFT_per tcon.doc
Importance:	High

Hi Lilya,

Attached are the labels for S36 and S32/S38. We have no additional edits to the label under S36.

There are three minor edits to the label for S32/S38. The Division has provided rationale/comments for these three changes in the attached label. Please let me know if there are any objections to these revisions. If not, please send me the final combined label in clean/tracked changes format to me via email and confirm that the final label in SPL will be submitted to the three pending supplements by Thursday morning.

Thanks,
Ayanna

Ayanna Augustus, PhD, RAC
Sr. Regulatory Health Project Manager
FDA/CDER/OND/ODEII/DAAAP
301-796-3980

29 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AYANNA S AUGUSTUS
09/17/2014