CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

021928Orig1s032

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-032

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021928/S-032

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-032

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

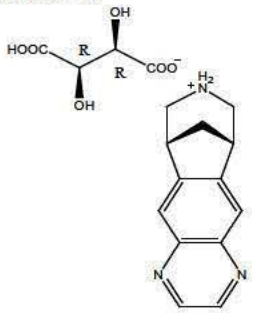
In case of overdose, standard supportive measures should be instituted as required.

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

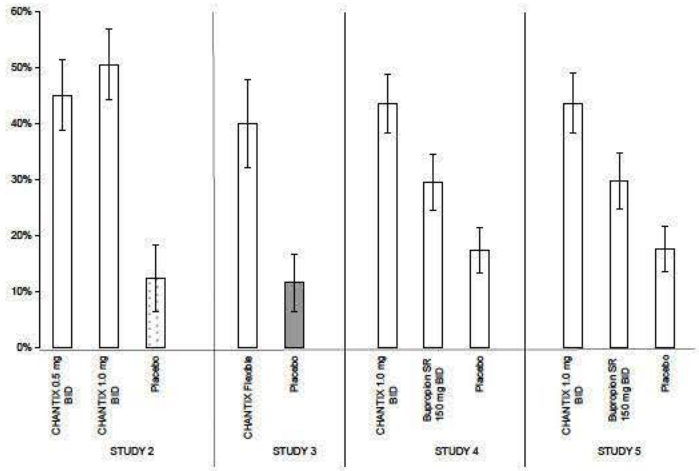


Table 6: Continuous Abstinence, Weeks 9 through 12 (95% confidence interval)

	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

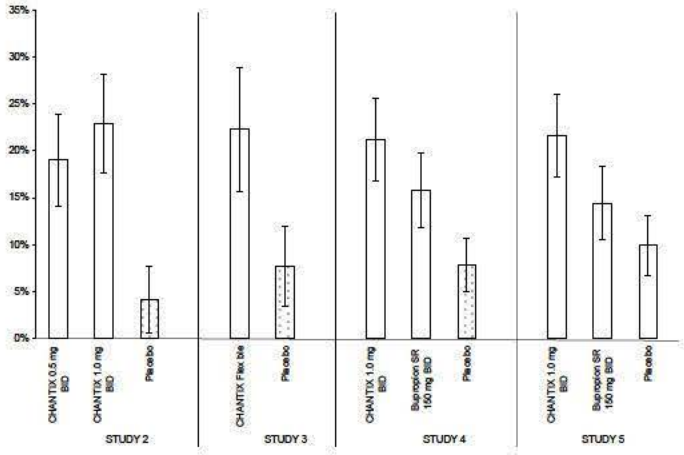


Table 7: Continuous Abstinence, Weeks 9 through 52 (95% confidence interval) across different studies

	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%)

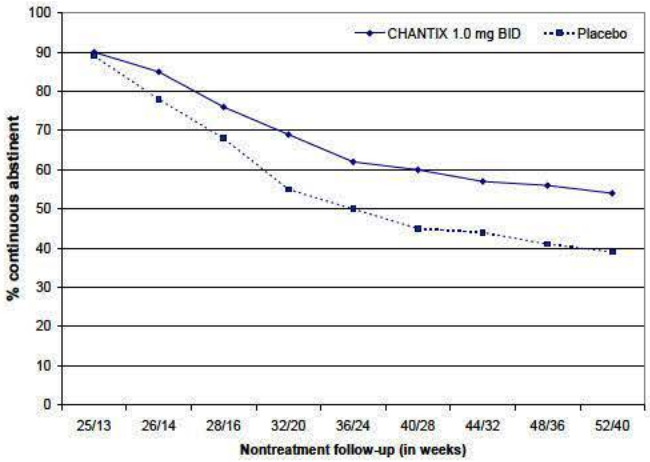
BID = twice daily

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.

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Division of Pfizer Inc, NY, NY 10017

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021928/S-032

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-032

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-032

MEDICAL REVIEW(S)

Medical Officer Review

Date	7/10/14
From	Celia Winchell, M.D.
Subject	Chantix-alcohol interaction
NDA # **Supplement#**	21-928 S-032
Applicant	Pfizer
Date of Submission	Response to Information Request: 8/14/13 Labeling Supplement: 10/24/13
Proprietary Name / **Established (USAN) names**	 CHANTIX (varenicline tartrate) tablet, film coated
Dosage forms / Strength	Oral Tablet
Indication(s)	Aid to smoking cessation treatment (approved)

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.

In May 2013, prompted by concerns raised by spontaneous adverse event reports and an inquiry from external stakeholders, DAAAP asked Pfizer to search their database for any cases that might point towards the potential for Chantix to reduce tolerance to alcohol.

A response to the information request was submitted in August 2013, followed by a labeling supplement in October 2013, in which Pfizer proposed to add the following statement to the Drug-Drug Interactions section of labeling:

(b) (4).

This review describes Pfizer's submission and conclusions and summarizes the review team's conclusions on the data submitted by Pfizer and on AERS cases analyzed by the Division of Pharmacovigilance II DPV2) in the Office of Surveillance and Epidemiology (OSE).

1. *Pfizer's Search Strategy*

Pfizer performed the search as described in the passage below:

As the first step to determine the overarching characteristics of alcohol-related adverse events (AEs), a text string search was performed in the Pfizer safety database, utilizing the words "alcohol", "etoh", "drunk", and "intoxication" , "ethanol", "hangover", "drinks", "wine", "beer", "cocktail", "spirit", "vodka", "gin", "whisky", "whiskey", "brandy", "port", "sherry". Based on the Preferred Terms (PTs) identified in the text string search, as well as an additional review of the PTs in MedDRA (version 16.0), PTs were selected to identify relevant cases involving alcohol for both the clinical and safety databases. In addition, the FDA-proposed PTs Alcoholic hangover, Binge drinking, Delirium tremens,

Feeling drunk, and Hangover were included in the clinical and postmarketing search for alcohol use cases.

Treatment Emergent AE data from all Phase 2-4 placebo controlled varenicline clinical trials completed as of 30 April 2013 were searched for the alcohol-related PTs selected as described above. The clinical trial data was further reviewed for information about a possible interaction between varenicline and alcohol using a text string search of investigator verbatim AE terms and investigator comments for action taken and causality, and Treatment Emergent Serious Adverse Event (SAE) narratives. Alcohol-related PTs, PTs in the Psychiatric Disorders System Organ Class (SOC) and other AEs of interest were selected for further discussion.

2. *Pfizer's Findings and Reviewer Discussion*

a. *Clinical Trials Database*

The clinical trial database identified 7 cases in varenicline-treated patients (N = 4823) and 3 in placebo-treated patients (N=3204). Pfizer provided the following table showing the preferred terms.

Alcohol-Related PTs of Interest Reported in 17 Placebo Controlled Phase 2-4 Varenicline Studies

PT	Varenicline N=4283	Placebo N=3204
	n (%)	n (%)
Any Alcohol-Related PT	**7 (0.15)**	**3 (0.09)**
Alcohol abuse	1 (0.02)	1 (0.03)
Alcohol intolerance	1 (0.02)	1 (0.03)
Alcohol poisoning	1 (0.02)	0
Alcoholism	1 (0.02)	0
Feeling drunk	1 (0.02)	2 (0.06)
Hangover	2 (0.04)	0

Source table: Appendix 2 (Table 1a SCSa3050444a) Subjects are only counted once per treatment for each row. Includes data up to 30 days after last dose of study drug. MedDRA (version 16.0) applied. Includes Protocols: A3051002, A3051007, A3051016, A3051028, A3051036 A3051037, A3051045, A3051046-48, A3051049, A3051054, A3051055, A3051072, A3051080, A3051095, A3051104, A3051115, and A3051122

The table below provides what little information was available about the use of alcohol and the AEs listed above.

Table 2. Treatment Emergent AEs of Interest Identified by the Search for Alcohol-Related Terms of the PTs, Investigator Event Terms and Comments

Subject ID/ Gender/ Age (Years)/Race/ Weight (kg)	PT/ INVESTIGATOR TERM	Causality Per Investigator Comment	Other Information Available
Varenicline			
Alcohol-Related PTs			
(b) (6) F/ 23 Y/ WHITE/ 62kg	Hangover/ HANGOVER	Other – too much alcohol	Included in Table 1 No further information available
(b) (6) M/ 25 Y/ WHITE/ 98kg	Hangover/ HANGOVER EFFECT	Other - new year's eve party	Included in Table 1 No further information available
(b) (6) M/ 41 Y/ WHITE/ 77kg	Alcohol intolerance/ INCREASED SENSITIVITY TO THE EFFECT OF ALCOHOL (PATIENT FELT IT TOOK A LESSER CONSUMPTION OF ALCOHOL TO EXPERIENCE ITS EFFECTS THAN PREVIOUSLY	Study drug	Included in Table 1 AE of Affect Lability reported the same day
(b) (6) M/ 60 Y/ WHITE/ 60kg	Alcoholism/ CRAVING FOR ALCOHOL	Study Drug	Included in Table 1 AE of Depression reported at the same time
(b) (6) M/ 45 Y/ WHITE/ 80kg	Alcohol abuse/ ALCOHOL ABUSE	Study drug	Included in Table 1 No further information available
(b) (6) F/ 38 Y/ WHITE/ 68kg	Alcohol poisoning/ ALCOHOL INTOXICATION	Other - associated with ingestion of alcohol	Included in Table 1 AE of Anxiety reported the same day
(b) (6) M/ 40 Y/ WHITE/ 63kg	Feeling drunk/ FEELING TIPSY	Study drug	Included in Table 1 No further information available
Other PTs of Interest			
(b) (6) M/ 53 Y/ WHITE/ 68kg	Disturbance in attention/ LACK OF CONCENTRATION Dizziness/ LIGHT HEADINESS	Other - alcohol related	AE of Affect Lability reported the same day
(b) (6) M/ 53 Y/ WHITE/ 79kg	Therapeutic response unexpected/ ALCOHOL APPETITE REDUCED (UNEXPECTED THERAPEUTIC	Study drug	No further information available

Table 2. Treatment Emergent AEs of Interest Identified by the Search for Alcohol-Related Terms of the PTs, Investigator Event Terms and Comments

Subject ID/ Gender/ Age (Years)/Race/ Weight (kg)	PT/ INVESTIGATOR TERM	Causality Per Investigator Comment	Other Information Available
	EFFECT)		
Placebo			
Alcohol-related PTs			
(b) (6) F/ 51 Y/ WHITE/ 56kg	Feeling drunk/ BUZZ FEELING	Study drug	Included in Table 1 No further information available
(b) (6) M/ 42 Y/ OTHER/ 67kg	Feeling drunk/ BUZZ FEELING Alcohol intolerance/ ALCOHOL INTOLERANCE	Study drug	Included in Table 1 No further information available
(b) (6) M/ 64 Y/ WHITE/ 61kg	Alcohol abuse/ ALCOHOL ABUSE	Other - underlying history of alcohol abuse	Included in Table 1 Narrative available for the SAE of Intentional Self-Injury reported for same subject (in Section 3.3)
Other PTs of Interest			
(b) (6) M/ 44 Y/ ASIAN/ 73kg	Traumatic intracranial haemorrhage/ TRAUMATIC SUBARACHNOID HAEMORRHAGE	Other-traumatic subarachnoid haemorrhage due to a fall following alcohol drinking	SAE. Narrative available (in Section 3.3)
(b) (6) M/ 68 Y/ WHITE/ 77kg	Memory impairment/ WORSENING MEMORY	Other illness-underlying medical condition including aging, alcohol intake, throat cancer, stress and anxiety	No further information available
(b) (6) F/ 30 Y/ WHITE/ 92kg	Anxiety/ ANXIETY	Other-drinking alcohol caused one day of anxiety	No further information available

Source: Appendix 3 (Listing 1a, SCSa3050444a); Appendix 4 (Listing 2a, SCSa3050444a); Appendix 5 (Listing 4a SCSa3050444a)
Y=Years; M=Male; F=Female; AE=Adverse event; SAE=Serious Adverse Event

The investigator verbatim for varenicline subject (b) (6) notes an "increased sensitivity to alcohol (patient felt it took a lesser consumption of alcohol to experience its effects than previously)." It should be noted that Pfizer's clinical trial database does not appear to capture patient verbatim reports of adverse events, only an investigator verbatim report, and that the case report forms often contain only a MedDRA term and a severity assessment, such as

"patient reported moderate insomnia." Therefore, there is often too little information to determine the circumstances of a particular event.

Five SAEs were identified in the text string search (2 varenicline and 3 placebo), but review of these cases revealed that none were examples of reduced tolerance to alcohol in the setting of Chantix use.

b. ***Post-Marketing Data***

Pfizer described their approach to the post-marketing data as follows:

With respect to the postmarketing review, cases reporting PTs associated with alcohol consumption, as well as cases for which alcohol (ethanol) was coded as a co-suspect medication were reviewed.

Using a lock date 4/30/13, the search returned 720 cases which Pfizer individually reviewed. Among these were 34 cases describing reduced tolerance to alcohol. Among them, the following terms suggesting potentiation of alcohol effects were reported more than 3 times:
Alcohol intolerance (18)
Feeling drunk (9)
Amnesia (5)
Feeling abnormal (5)
Loss of consciousness (5)
Alcohol interaction (4)

Information on the quantity of alcohol consumed was reported in 22 cases, in 19 instances, the patient had consumed 4 drinks or less. The 34 cases provided 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. Positive de-challenge was reported in two. Many of the narratives make it clear that the consumer was calling to inquire about, or report upon, what he or she perceived to be an interaction between Chantix and alcohol.

Pfizer concluded, however, "These cases generally described getting drunk on small quantities of alcohol, and in a few cases memory impairment or amnesia was also described. Overall, the events in this dataset could not be clearly attributed to the combining of varenicline and alcohol as they are known to be independently associated with either one of them or both, and do not exceed the type and severity of the AEs documented in the varenicline current US package insert (USPI)."

Pfizer also separately described 108 cases that involved violence, which they divided into 52 cases with self-directed violence, 46 involving violence to property or to others, and 10 involving both.

Among 52 the cases of self-harm, 17 involved relevant events occurring in a close temporal relationship to alcohol consumption. Pfizer noted "Among these 17 cases, the quantity of alcohol consumed was reported in 4 cases, and was described as 2 beers, 2 units of alcohol, 3 cocktails, and 4 to 5 glasses of wine or more; in 1 additional case, it was reported that the

patient had been drinking heavily at the time of the event. The duration of varenicline therapy at the time of the relevant event(s) was reported in 8 of these 17 cases, and was reported as 15 days, 2.5 weeks, 1 month or less, 1 month, 5 weeks, 6 weeks, 3 months, and 3 to 4 months."

Among the 46 cases of other-directed violence, 12 did not involve drinking at the time of event, or mentioned alcohol as secondary to other events. Among the remaining 34 cases, there were 16 cases where information on the quantity of alcohol consumed was reported, with the following descriptions:

- 2 beers
- 2 drinks
- a few drinks (2)
- a few glasses of wine
- 3 beers
- 4 - 5 beers
- 4 beers
- 6 beers
- 7 - 8 drinks
- 7 beers
- was drinking heavily
- half a bottle of whiskey
- drank a lot

"The duration of varenicline therapy at the onset of the relevant events was reported in 10 of these 16 cases, and was reported as less than 1 day in 1 case, 2 days to 1 week (2, 4 or 7 days in 1 case each), 10, 14 or 18 days (1 case each), 5.5 weeks (and 4 days post therapy), 7.5 weeks, or was described as a few months."

Several cases reported amnesia for the events.

Pfizer acknowledges "In 6 cases, incidents of outwardly directed violence were clearly described in which the patient consumed a relatively small amount of alcohol and developed violent behavior towards others and/or property, and in many of these cases, the patient had no memory of these events. In 1 of these cases, it was specifically reported that the patient was "not himself" and, in 1 other case, the behavior was described as "totally out of character". In these instances, a role for the combination of varenicline and alcohol in the onset of the events could not be ruled out."

Of 10 cases involving both self-directed and other-directed violence, 2 cases reported violent acts following consumption of relatively small quantities of alcohol.

In total, the post-marketing cases provide multiple examples of exaggerated and uncharacteristic response to alcohol including at least 8 cases of violent behavior involving consumption of small amounts of alcohol.

Illustrative cases are included in the Appendix.

c. Literature review

To identify the clinical literature articles that discuss potential interactions of varenicline and alcohol, Pfizer performed a search was on 17 June 2013 in PubMed using the search string *(varenicline OR Chantix OR Champix) AND (alcohol OR ethanol OR intoxicat* OR ETOH OR drunk)*; a total of 61 publications were identified. Among the 61 publications, there were 7 publications involving clinical studies in humans, 3 case reports, and 2 epidemiology studies.

Pfizer reported that the remaining 48 publications were either animal studies or did not offer information on the topic of varenicline and alcohol interaction or safety. A separate literature search specifically designed to identify non-clinical literature articles was conducted on 12 June 2013, which captured 63 publications.

Pfizer noted that "there was extensive data reported in the literature from animal models demonstrating a potential interaction between alcohol and varenicline at both neurophysiological and behavioral levels, [but] the specific mechanism of the interaction has not been fully elucidated. Further, the nature of the observed interaction is variable and occasionally contradictory across studies."

At least one study demonstrated that varenicline increased alcohol-induced ataxia and decreased locomotor activity in C57BL/6J mice (Kamens et al., 2010)[i], which is consistent with the experiences of the reporters in the post-marketing database.

One article (Kaminski and Weerts, 2014)[ii], reporting on a study of the effects of varenicline on alcohol self-administration in baboons, summarizes the literature on the interaction as follows:

One of the proposed behavioral mechanisms underpinning varenicline effects on alcohol self-administration is a decrease in the reinforcing efficacy of alcohol due to an increase in the aversive and/or sedating effects of alcohol. In C57BL/6J mice, varenicline increased EtOH-induced ataxia and decreased locomotor activity (Kamens et al., 2010). In human subjects, which to date have all been alcohol-drinking smokers, pretreatment with varenicline has produced increases in the sedating effects of alcohol (Fucito et al., 2011)[iii], decreases in alcohol positive subjective effects (Childs et al., 2012[iv]; McKee et al., 2009[v]), and increases in ratings of dysphoria (Childs et al., 2012). In rats, high doses of varenicline (3.2 to 5.6 mg/kg) have been reported to disrupt responding for both alcohol and food (Ginsburg and Lamb, 2013[vi]). While the present procedure did not include a direct measure of aversive effects, in the present study, 0.32 mg/kg when delivered BID, and to a lesser extent when delivered daily, produced increases in latency to initiate drinking and suppression of drinking in the first bout in both groups, suggesting that nonspecific aversive effects cannot be ruled out

Pfizer also noted that "the majority of the 7 clinical trial publications identified in the clinical literature review do not appear to support an exacerbation of alcohol consumption during varenicline treatment; on the contrary, most of the trials showed either statistically significant or a trend towards reduction in alcohol consumption and cravings."

It must be noted that the concern here is not that varenicline increases alcohol *consumption*; it is that it increases the *effects* of alcohol. If true, this could certainly lead to reduction in alcohol use because individuals often titrate their alcohol use to a particular level of subjective effects.

The two epidemiology studies submitted did not shed light on the potential of varenicline to reduce tolerance to alcohol.

3. DPV Findings

DAAAP requested that the Office of Surveillance and Epidemiology's Division of Pharmacovigilance-2 review the FAERS database to identify cases related to the possible interaction between alcohol and varenicline.

DPV-2 summarized their findings as follows:

> We found 48 non-fatal FAERS cases of patients on varenicline who also consumed alcohol and experienced adverse events involving aggressive behavior (n=37) or a decreased tolerance to alcohol (n=11; felt more inebriated). The aggression cases included descriptions of patients inflicting physical harm against persons/property; some involved law enforcement and one involved a motor vehicle accident. One of the decreased alcohol tolerance cases described a motor vehicle accident with police arrest and a second described a facial injury. In most (n=8/11; 73%) of the decreased tolerance cases and in almost two-fifths (14/37; 38%) of the aggression cases the patient did not remember the experience. Overall almost two-fifths (18/48; 38%) of the case series was reported by a healthcare professional (vs. consumer), which supports the validity of the data.
>
> …Some subsets were 100% individually reviewed and some were sampled. This ultimately allowed us to review more than three-fifths (388/624; 62%) of the original crude count. Because *decreased alcohol tolerance* involved sampling, we expect there to be a few additional such cases amongst the unreviewed FAERS reports.

DPV-2 recommended that information be added to the Chantix Warning section informing prescribers that the concomitant consumption of alcohol and Chantix may result in aggression and potentiation of alcohol's intoxicating effects.

4. Actions by Other Regulatory Agencies

During the course of this review, the team became aware of the following actions taken by other global regulatory bodies:

Health Canada: Changes to the Canadian product monograph, implemented in March 2014, include statements that "Patients should be advised that alcohol intake may increase the risk of experiencing psychiatric adverse events during treatment with CHAMPIX."

Medsafe New Zealand: In June 2013, New Zealand's Centre for Adverse Reactions Monitoring placed varenicline in its "medicine monitoring scheme," published a Medsafe monitoring communication to alert healthcare professionals that Medsafe was seeking additional information on this issue, and requested additional information from Pfizer about varenicline/alcohol interactions. In May 2014, the Medicines Adverse Reactions Committee discussed the submitted

information and recommended that Medsafe request the sponsor of Champix to update the data sheet to include the following wording in the interactions section:
"Although clinical data do not identify a pharmacokinetic interaction between varenicline and alcohol, there have been occasional reports of adverse neuropsychiatric events or reduced alcohol tolerance in patients drinking alcohol during varenicline treatment."

EMA: EMA has noted cases of varenicline/alcohol interaction in the PSURs and has requested Pfizer submit a cumulative analysis and discussion, along with proposals regarding any changes to the SPC. This assessment is to be submitted shortly and EMA plans to complete their review in the fall.

5. Summary and Conclusions

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.

Pfizer has concluded that the events described in these cases are subsumed within the events already warned about in section 5.1 Neuropsychiatric symptoms and suicidality. However, our reviews (DAAAP and DPV) indicate that there are two distinct types of cases. One group describes a potentiation of the intoxicating effect of alcohol, and the other group describe neuropsychiatric events temporally associated with alcohol use. The former group are 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.

APPENDIX

Illustrative cases from Pfizer's post-marketing database are shown below. The AER number is Pfizer's identifier. Yellow highlighting draws attention to text relating to potentiation of alcohol's intoxicating effects. Green highlighting identifies re-challenge/de-challenge information. Some cases have been edited or truncated to remove irrelevant text.

AER Number (b) (6)
This consumer reports that her 49 year old sister started taking Chantix (varenicline) 0.5 mg daily for smoking cessation on 21Oct2006. The patient has a past history of increased consumption of alcohol over the past year. There are no relevant concomitant medications. There is no relevant past drug history. On 22Oct2006, the patient called her sister stating that she drank 12 cans of beer and felt more "loaded" than usual. No labs have been done. As of 23Oct2006, it is unknown if the patient continues to take Chantix. Outcome of the events was unknown at the time of the report

AER Number (b) (6)
This female consumer of unknown age reports that she has been on Chantix (varenicline) for smoking cessation therapy, and missed a dose the day before reporting. On the same day, the consumer had a couple of drinks and felt "wasted out of my mind - and I never, ever get that way, which she feels was due to combining Chant x and alcohol. She also mentioned that she was so intoxicated that she wet herself, and was sick the following morning. No further information available.

AER Number (b) (6)
This 46-year-old female consumer reported that she began taking the Chantix (varenicline) starter pack on 27Aug2007 to quit smoking, and she drank alcohol, but had not had any alcohol for a while before 01Sep2007. The patient's relevant medical history included she was enrolled in a class for chemical dependency for alcohol, and normally having one beer would not affect her. The patient had no relevant past drug history and her relevant concomitant medications included Prozac and trazodone. The patient reported that on 01Sep2007, she could not locate her starter pack of Chantix, and she took a 1mg tablet instead of a 0.5mg tablet for one dose. On 01Sep2007, she had a beer, the beer affected her, and she suspected Chantix lowered her tolerance for alcohol. There were no relevant laboratory tests.
As of 02Sep2007, the patient continued Chantix, she planned to try to quit smoking on 03Sep2007, and the outcome of the events was unknown. Chantix was obtained in the USA. The patient was not enrolled in the GetQuit program.

AER Number (b) (6)
This consumer reports that her 64-year-old husband started taking Chantix (varenicline) 0.5 mg daily on 12Nov2007 for 3 days, followed by 0.5 mg twice daily for 4 days, followed by 1 mg twice daily thereafter, to stop smoking. On 20Nov2007, her husband consumed 1 gin and tonic, for an unknown indication. The patient had no relevant medical history of becoming very intoxicated, of becoming lightheaded, or of becoming forgetful after drinking just one gin and tonic. The patient had no relevant drug history. The patient takes the following relevant concomitant medication of low dose Nicorette gum (nicotine resin) while taking Chantix. On 20Nov2007, as her husband continued using Chantix 1 mg twice daily, he had one gin and tonic and after having this alcoholic beverage he became very intoxicated for a long period of time at least a couple of hours, he also became lightheaded, and then he became forgetful described as being almost demented. This reporter suspects that there is an interaction with alcohol that caused these events. There is no relevant laboratory data. As of 21Nov2007, her husband continues taking Chantix, her husband does not plan to drink any more alcohol while using Chantix, and all of the events have resolved. He does not belong to a smoking cessation support program. Reporter stated Chantix was received in the United States.

AER Number (b) (6)
This nurse practitioner reported that the 44-year-old female patient took Chantix (varenicline) in Sep2007 at a dose of 1mg twice daily, for smoking cessation, felt the effects of "ETOH" quickly on Chantix therefore stopped the drug. The patient reported that after 1 beverage she felt like she'd had 5-6 beverages. This feeling happened on 2 occasions 7 weeks apart. The patient had no relevant laboratory testing. The event abated after the Chantix was stopped and it was unknown if the event would return if the medication was re-started. As of 21Nov2007 the patient was not taking Chantix and the event resolved.
Follow-up (25Jan2008):
This nurse practictioner reported this 43-year-old female consumer was started on Chantix (varenicline) 1 mg orally daily on 01Aug2007. On 01Aug2007, this patient felt dizzy, nausea "drunk" on several

occasions after having 1 to 2 alcoholic beverages while on Chantix. In 2007, with stopping of Chantix, her events resolved. In mid Sep2007, Chantix was discontinued and her events resolved.
Follow-up status: case closed. (25Mar2008)

AER Number (b) (6)
This 55 year old male consumer was started on Chantix (varenicline) 1 mg twice a day, 2 months ago in Sep2007 to quit smoking. This consumer reports he normally has a glass or 2 of wine every evening and many evenings he will also have a glass of Sambucca. In the past, he has been on Buspar and this medication mellowed him out. In 2007, after starting on Chantix, he found when he had his evening wine or Sambucca, the feeling he was looking for was intensified, it felt good, felt nice and made hime relax. He suspects taking the Chantix with one glass of wine, made it feel like he had had 3 or 4 glasses of wine. About 1.5 to 2 weeks ago in Nov2007, he was out to dinner and he had a couple of glasses of wine and it made him a bad person described as an attitide change. He experienced intensified depression and suicidal thoughts in Nov2007. A couple of days ago in Nov2007, he saw an advertisement on television that made him realize he should not drink while taking Chantix. Two days ago in Nov2007, Chantix was stopped due to these events and the events resolved. A couple of days ago in Nov2007, Amoxicillin was started to treat a tooth infection. On 22Nov2007, he had a glass of wine with dinner and it felt normal. There is no relevant laboratory data. As of 23Nov2007, he is off the Chantix. He found the Chantix was a great drug by itself, it was calming and took away his cravings for cigarettes, but he found the Chantix with alcohol intensified the feelings he got with alcohol.

AER Number (b) (6)
This nurse reports that this female patient aged about 40, who is also a nurse, received Champix (varenicline) of unknown dose for smoking cessation for 5 weeks and has followed the initial titration and stopped smoking. The reporter was not aware whether the patient was receiving any concomitant medications. The patient has found that when she has drunk alcohol during treatment with Champix she has felt excessively drunk for the amount of alcohol she has consumed. This has happened twice, a few nights ago she had drunk 2 glasses of wine and felt excessively drunk, and the people she was with made comments as to how drunk she was. On another occasion, the patient had drunk about 3 glasses and the same thing happened. The action taken with Champix in response to the event and the outcome of the event was unknown at the time of the report. No further information was provided.

AER Number (b) (6)
19-year-old male patient reported he started Chantix (varenicline) to take 0.5mg daily for 3 days then 0.5mg two times daily for 4 days then 1mg two times daily to stop smoking cigarettes on 19Dec2007.
He had a … history of being able to drink a 12 pack or 20 pack of beer before feeling drunk. He has a history of being high on weed before and a history of his teeth never hurting before. He had a relevant past drug history of having taken both prednisone (manufacturer unknown) and Zithromax (azithromycin) prior to Chantix without any problems. His relevant concomitant medications included Zithromax and prednisone (manufacturer unknown) 20mg two times daily for 5 days that were both started on 19Dec2007 at the time he started Chantix. The patient started Chantix on 19Dec2007 and did well until 22Dec2007 when the dose increased to Chantix 0.5mg two times daily. On 22Dec2007 his teeth hurt, he felt irritable, felt weird, felt a weird kind of buzz. On 22Dec2007, after his teeth hurting, feeling irritable, weird, and feeling a weird kind of buzz he went out and had 2 beers and felt almost drunk after only 2 beers. ...

AER Number (b) (6)
This 55-year-old female patient reported that she took Champix (varenicline) "for about 2.5 weeks" for smoking cessation therapy in Dec2007. She did not use any concomitant medication. The woman had no relevant medical history and had not suffered depression before. Her menopause was about five years ago. During Champix therapy the female patient experienced aggressive and depressive mood and a weight gain of about 3 kg. She got drunk easily when she had 0.125 ml of wine with her meal. Due to these events she permanently discontinued Champix at the end of Dec2007. At the time of this report she had not fully recovered.

AER Number (b) (6)
The wife of a 44 year old male patient, reports that her husband, initials ME, date of birth 06APR1964 who is receiving Champix (varenicline tartrate), dose and indication unspecified, for approximately seven weeks, experienced decreased libido and becomes intoxicated on three glasses of beer. His wife reports that he can usually drink a lot more beer before becoming intoxicated, but since he has been taking Champix he appears affected by alcohol a lot quicker. The patients concomitant medication is aspirin (unspecified). No further information is available.

AER Number (b) (6)
This 55-year old female consumer reports that she was started on Chantix (varenicline) 0.5 mg once daily for 3 days then 0.5 mg twice daily for 4 days then 1.0 mg twice daily on 25Mar2008 to stop smoking.
Relevant medical history includes: she takes Zoloft for her compulsive cleaning and also for depression or sadness associated with an empty nest feeling when her last child went to school. ,,,. She usually has a couple of drinks on Wednesdays when she gets together with her friends. …The first day she took the Chantix on 25Mar2008 her palms were sweaty, she had a headache. She was

(b) (6) described as "a feeling like she could have jumped out of her skin". The nervousness kicked in about 2-3 hours after taking the Chantix. The second day she took the Chantix on 26Mar2008 she
experienced the same symptoms at work but she felt better at night when the Chantix began wearing off. On 26Mar2008 she had a couple of drinks with her friends and the alcohol seemed to affect her
more than usual when she was taking the Chantix. The third day she took Chantix on 27Mar2008 she experienced the same symptoms and she also felt like she was "stupid" or stoned or hazy because she
did not understand jokes that people were telling her. She felt that the Chantix was affecting her thinking ability. She took the Chantix this morning and she is experiencing sweaty palms and she is starting to
feel nervous but not that much because the Chantix hasn't kicked in yet today. The stupid, stoned or hazy feeling has not occurred yet because she only took the Chantix 45 minutes ago. She has had a
headache everyday for the past 3 days but it is unknown if she has a headache today on 28Mar2008. She continued on Chantix as of 28Mar2008 but is leery of increasing her dose to
the 0.5 mg twice daily dose since she had all of these symptoms with just taking 0.5 mg once daily and she feels that the 0.5 mg twice daily dose might be too strong for her.

AER Number (b) (6)
A pharmacist reports that a female patient, in her late 60s to early 70s, started receiving therapy with Champix (varenicline tartrate), dose and indication unspecified, with the last dose of "starter pack" on
Wednesday (26Mar2008) or Thursday (27Mar2008) of the week prior to reporting. After drinking two to three glasses of wine on Sunday night (b) (6) 2008), she apparently was admitted to the hospital after
"running into a hotel", being incoherent and babbling. The pharmacist was not certain of all the events as the patient herself was unclear of the sequence of events. The patient had also been using a "weed
killer" at some stage during the weekend. No further information was available.
Follow-up (30May2008):
The same pharmacist reports that the female patient, aged over 60 years, who was taking Champix orally, experienced confusion and amnesia requiring admission to the accident and emergency
department, around (b) (6) 2008. She had had "two white wines" at a social gathering, and could not recall how they got to the hospital, or the events leading up to the admission. The patient did not receive any
treatment, only observation. Champix was discontinued, and not reintroduced, and the events resolved. The patient has no ongoing issues, and has stopped smoking. No confirmatory tests were performed.
Concomitant medications included Fosamax (alendronate sodium) 70mg, one oral dose, weekly; Monoplus (fosinopril sodium; hydrochlorothiazide) 20/12.5 one dose daily. The pharmacist believes the
events were related to Champix. No further information provided.
Company Clinical Evaluation
The events confusion and amnesia are assessed as not related to varenicline.

AER Number (b) (6)
This female consumer (age unknown) reported that she started to take Chantix (varenicline) with unknown dosage for unknown indication from Nov2007-Dec2007. The relevant medical history, past drug,
concomitant drug and lab data were unknown. She stopped it in Jan2008 because she was experiencing side-effects while on Chantix. Currently she was visiting a psychiatrist and a medical doctor since
Feb2008. She said that Chantix was "ruining her life and career". She said that there was "no joy" in her life. The outcome of the event was unknown.
Follow-up (25Apr2008):
This 55-year-old female consumer reported from the end of Nov2007 through Jan2008 she took Chantix (varenicline) 0.5mg orally daily with a planned increase to 1mg twice daily to stop smoking. Relevant
medical history is negative for personal or family history of emotional or psychiatric, mental health problems, depression, trauma, other disease, or emotional or mental problems with previous attempts to quit
smoking. ...Relevant medication history includes quitting smoking a few times for 3-4 months at a time using patches and never had any mental
side effects. She reported she quit smoking within 2 weeks of starting Chantix. She reported she felt great and didn't realize anything was happening when she was taking Chantix. She reported on an
unknown date in 2007 less than a month after starting Chantix, she started to have behavioral changes descr bed as knowing she shouldn't say certain things but can't keep herself from blurting them out,
misbehaving, her behavior changes described as she became more aggressive and combative and nasty to people, being disorganized and can't get anything done because of being disorganized, going out
to the garden and would stare at the shed for 10 minutes until she realized "wow", and blowing all her money when she knows she should be putting money away such as spending $1000 here and $2000 there - the
behavioral changed have been ruining her career and her boss re-wrote a review and trashed her mainly based on her behavior; she couldn't drink alcohol on Chantix described as went to a luncheon for
work and had not more than 2 glasses of wine, probably not even a full 2 glasses of wine in a 3 hour period, and got trashed; she was depressed descr bed as watching a John Wayne movie and boo-hooing,
like it sucked the joy out of her life, didn't enjoy being with her grandchildren, gets so down, or would like to be happy again; she was experiencing nightmares that were more like anxiety kind of dreams;
when she was awake she was seeing things, also described as dreams while she was awake, would open a door and expect to have someone on the other side ready to kill her, spooky stuff, would be in her

bathroom getting ready for work and feel like someone was staring at her from around the corner, or having visions and premonitions; she wasn't able to rest also described as would go all day long and
couldn't sit down, woke up frequently, woke every 1-5 hours after going to sleep, woke a few times each night; and thought she went crazy described as was hearing whispering and all of the sudden would
realize it was me, or trying to keep it hidden; she called a psychiatrist through her health insurance and was relieved to find these events were side effects from Chantix and weren't her. She stopped Chantix
in Jan2008 because of the events

AER Number (b) (6)
A pharmacist reported to a Pfizer sales representative and a physician reported to a Pfizer sales representative that this currently 39-year-old male patient has a medical history of nicotine dependency
starting around 1989 and smoked 40 cigarettes/day for about 20 years. He also has a medical history of insomnia and depression. …. In Apr2007, the patient was prescribed oral zopiclone (AMOBAN) 10 mg tablets, one tablet per day and oral brotizolam (LENDORMIN) 0.25 mg tablets, one tablet per day for his insomnia. He was also prescr bed
paroxetine hydrochloride (PAXIL) daily for depression in that same month. The PAXIL was discontinued in 2008 because his depression resolved. The patient was referred to the physician's clinic for
insomnia in autumn of 2008. On 18Oct2008, the patient started taking oral varenicline tartrate (CHAMPIX) , 1 mg tablets daily for nicotine dependence. On 01Nov2008 the patient experienced aphose,
dizziness, feeling queasy and dyspnoea (choking sensation in the precordial region) just once while driving. In Nov2008 the patient developed alcohol tolerance and complained of it on 29Nov2008. He
reported to the physician that he gets drunk more easily than before and that he does not take sleeping pills before drinking. He complained to the pharmacist that his alcohol tolerance was lowered on an
unspecified date, while taking CHAMPIX, AMOBAN 10 mg/day and LENDORMIN 0.25 mg/day. He explained that the amount of his alcohol intake was reduced and he felt an irresistible drowsiness after
drinking alcohol. In Oct2008, he experienced a coma for the first time. He fell into a drunkenness soon after drinking and did not notice that he was sleeping. He also had a problem that he fell asleep at a
banquet. He was tired from work and experiences this symptom especially on weekends. His physician instructed him to continue taking CHAMPIX, giving priority to smoking cessation. The patient did no
t resume smoking before the onset of these events. The patient's concomitant medications include an use of an unspecified dermatological drug. The event alcohol tolerance lowered resolved without any
treatment in Nov2008. The outcome of events aphose, dizziness, feeling queasy, and dyspnoea resolved on 02Nov2008 while the administration of CHAMPIX, AMOBAN and LENDORMIN was continued
unchanged. On (b) (6) 2008 the patient had a Tobacco Dependence Screener (TDS) test (results 9) and his expiratory concentration of C02 was 37, and on (b) (6) 2008 his expiratory concentration of C02
was 7. The reporting pharmacist classified the events as non-serious and assessed them as probably related to CHAMPIX, AMOBAN and LENDORMIN. The reporting physician reassessed alcohol
tolerance lowered as possibly related to CHAMPIX and probably related to AMOBAN and LENDORMIN. He also classified aphose, dizziness and feeling queasy and dyspnoea as non serious and possibly
related to CHAMPIX, The physician commented that somnolence and lethargy might have appeared as adverse drug reaction to CHAMPIX, AMOBAN and LENDORMIN.

AER Number (b) (6)
An internist reports to a Pfizer sales representative that a 41-year-old male patient was administered a regular course of varenicline tartrate (CHAMPIX) once daily at a dose of 0.5 mg/day on 21Jan2009
through 23Jan2009. The dose of varenicline was 1 mg/day 2x/day on 24Jan2009 through 27Jan2009, and 2 mg/day 2x/day after 28Jan2009 for smoking cessation therapy. CHAMPIX (varenicline tartrate)
was administered for nicotine dependence. The patient had smoked 60 cigarettes a day for 22 years before smoking cessation therapy. On 24Jan2009, the event of abnormal behaviour developed as
descr bed that the patient drunk about 450 mL of shochu (distilled spirit) at evening mealtime (he was normally having 600 mL of shochu at evening mealtime) and unusually got excited and pushed his wife
who was near him. He had not behaved violently before even when he had a large amount of alcohol. The patient himself was surprised very much. Later, the patient reduced the amount of alcohol intake
and was continuously taking varenicline. Since 30Jan2009, smoking cessation has been continued. … On
18Feb2009 (not 19Feb2009) the dose of varenicline was reduced from 2 mg/day 2x/day to 1 mg/day 2x/day due to the event "sleep loss"
and the patient continued daily alcohol (shochu) intake at 360 mL and no event of abnormal behaviour developed again after 24Jan2009.. ..

AER Number (b) (6)
A 31 year old female patient of unknown race started to receive varenicline (CHAMPIX) 1 mg unit dose on 27May2009 for smoking cessation therapy. On 09Jun2009 the patient
suffered anxiety, was tearful, feelings of depression and became very drunk on only a very small amount of alcohol. Four weeks later, the patient was recovering. Varenicline was permanently withdrawn as a
direct result of the events on 28Jun2009. The reporter considered anxiety, was tearful, feelings of depression and became very drunk on only a very small amount of alcohol to be serious due to being
medically significant as the patient was very down, had anxiety and symptoms of depression.

AER Number (b) (6)
A 37 year old female patient of unknown race received varenicline (CHAMPIX) 1mg twice daily dose from 07Jul2009 for smoking cessation therapy. On 17Jul2009 the patient after one and a half glasses and several sips of champagne felt really really drunk (alcohol intolerance) and uncoordinated and can't remember anything. No action was taken with varenicline in response to the events and the patient recovered on 18Jul2009. It was unknown if the patient was treated for the events. The reporter considered the events to be serious as they caused persistent or significant disability/incapacity and were medically significant.

AER Number (b) (6)
This 43-year-old female consumer of an unknown race reports that she started to receive varenicline (CHANTIX) ".05" mg orally twice a day to stop smoking on 14Mar2009. The consumer had a relevant medical history of being a social drinker who could tolerate alcohol and also knew when to stop before getting to a point of intoxication. The consumer reported that she did not have a drug or alcohol problem. Her relevant concomitant medications and past drug history were unknown. The consumer stated that she went out with her friends on 20Mar2009, the seventh day of varenicline treatment and her last day of smoking, and took her night time dose a couple of hours before she went out. She stated that she only drank a few drinks, maybe four beers in about a three hour period, and she does not have a low tolerance of alcohol either normally. The consumer reported that all of a sudden she started experiencing "the effects of being overly drunk but wasn't, there would be no possible way". She stated that she experienced loss of memory "except for bits and pieces when reminded the next day by the friends" she was with. She also stated that she blacked out in the club restroom and vomited several times there and on the way home. The consumer also reported that she could not wa k on her own without help from someone to lean on and fell a few times. She further reported that she woke up the next morning in bed but didn't remember how she got there or got home or got out of the restroom in the club. She also stated that she has never felt like that in her entire life and it was beyond drunk. The consumer was taking varenicline for a week at the time of this reaction. The consumer reported that If it were only on the warning label along with other dangerous side effects it would not have happened because she would have read the side effects. The consumer stated she did a search on the internet to see if anyone else had experienced this besides her because there was no warning on the varenicline label about poss ble side effects of mixing alcohol and varenicline that it may intensify the alcohol effects severely. She reported that she found others that have had the same experience as her by only having minimal alcohol but having the effects of massive amounts. The consumer stated that she was thankful that she was with friends that night and not alone and she "could be dead now or someone else could". She stated that she does not know why people are not warned of this dangerous effect and wanted to know how one can go about getting a drug l ke this to place a warning on their label. She stated "that was extremely dangerous what I experienced and I would hate for another unknowing person out there to experience the same thing because there is no warning" on varenicline's label. The consumer further stated "that was definitely not me that night" and "it was like someone drugged me but no one did" it was varenicline. It was unknown if there was any relevant laboratory data or if the patient was diagnosed. The consumer discontinued varenicline therapy on 24Mar2009 for an unknown reason.

AER Number (b) (6)
This is a spontaneous report from the contactable partner of a male patient, age unspecified, who started to receive varenicline tartrate (CHAMPIX) on 31Jan2010 (dose and indication unspecified). The patient's father passed away unexpectedly in Apr2009, and the patient may have been experiencing depression. During the week prior to reporting, the patient became progressively depressed. He also has been more susceptible (feeling drunk) to alcohol since starting varenicline. He normally can consume about half a dozen of beers and not feel drunk. On 03Feb2010, the patient consumed half a dozen of beers and one gin and tonic over a period of seven hours and he could not walk or talk and experienced urine incontinence. On 06Feb2010, the patient attended a family BBQ and did not have much to drink; he got up on 07Feb2010 at 02:30 with sweats and chest pain. He got up again at 05:00 and packed his bag and walked out of the house. The reporter is not sure where he was and he was not answering his calls. She thinks that he was at his family home. The doctor who prescribed varenicline had not asked the patient about a history of depression, or the possible use to alcohol with varenicline. The action taken with product varenicline and outcome of the event at the time of the report was unknown.
Follow-up status: Case closed 08Feb2010.

AER Number (b) (6)
This is a spontaneous report from a contactable smoking cessation advisor via a Pfizer sales representative. A 42 year old white male patient of unknown race received varenicline (CHAMPIX) 1mg twice daily from 30Mar2010 as smoking cessation therapy. … On an unspecified date, in week ten of treatment, the patient took an evening dose of 1mg at about 4pm with a pint of lager on an empty stomach. The patient next remembered waking up in a field 100 yards from the pub, two hours after leaving the pub. The events occurred on the 03Jun2010 and the patient stated that he did not remember anything about how he ended up in the field but he appeared unharmed. The patient was not injured and did not believe that he had his drink spiked. The patient stated that when he was at home and he had a few drinks of lager

he had noticed that he appeared more affected by it since being on varenicline. The patient was continuing with varenicline as of 10Jun2010 and stated that he would ensure that he did not consume alcohol with it again. The patient had tolerated varenicline and had not experienced any other side effects. No action was taken with varenicline in response to the events and the patient recovered from the events on the same day. The reporter considered the events to be medically significant and therefore serious. The reporter considered there to be a reasonable possibility that the events were related to treatment with varenicline.

AER Number (b) (6)
A 61-year-old male patient (race unknown) started to receive varenicline tartrate (CHAMPIX) orally 0.5 mg once daily from 15Oct2010 to 17Oct2010, at 0.5 mg twice daily from 18Oct2010 to 21Oct2010, and 1 mg twice daily from 22Oct2010 to Dec2010 for smoking cessation therapy. The patient had a past history of gastric cancer, smoked 60 cigarettes for 44 years, and drank a half bottle of whisky a day. On 15Oct2010, the patient was started on varenicline tartrate at another hospital. In Nov2010, mild hepatic function abnormal was pointed out. In Dec2010, the patient became strongly aggressive which was obviously noted by other people. Especially after alcohol intake, he screw with and complained to others. He repeatedly had memory gap after alcohol intake, and noticed on the following day of alcohol intake that he had fallen and sustained injuries. He actually had traumatic injuries on his head and face but his memory about these events was uncertain. Before initiation of varenicline tartrate, he relatively had a high tolerance for alcohol and he did not behave l ke that. The internist considered that these changes might be due to varenicline tartrate, and varenicline tartrate was discontinued on 19Dec2010. After discontinuation of varenicline tartrate, the aggressive character improved, while the state of alcohol tolerance lowered persisted for a while. The outcome of the events are as followed: Aggression resolved on Jan2011, Alcohol tolerance lowered resolved on Mar2011, Amnesia transient resolved on Mar2011, Hepatic function abnormal resolved at the end of Dec2010. Fall and traumatic injury were classified as non-serious and resolved in Dec2010.

AER Number (b)
An approximately 35 year-old female patient of unknown race started to receive varenicline tartrate (CHAMPIX) dose unknown, from an unknown date and for smoking cessation. Concomitant medication included unspecified SSRIs. Medical history included depression. From an unknown date, in excess of 12 weeks use of varenicline tartrate, the patient experienced elevated mood and also reported a reduced capacity to drink alcohol. She had stated that she was unable to drink the same amount of beer she used to.

AER Number (b) (6)
A 49-year-old male patient of an unspecified ethnicity started to receive varenicline tartrate (CHAMPIX), starter pack .. for smoking cessation in Nov2011. The patient medical history was unknown. The patient had no previous psychiatric history. .. On 18Nov2011 (half way through the first supply of varenicline tartrate) the patient had consumed approximately one bottle of alcohol (wine) during dinner and became totally drunk, felt weird, panic and severe anxiety for approximately six hours. This had never happened before from one bottle of wine. On 05Dec2011 the patient began the repeat of varenicline tartrate 1mg tablets. He had increasing panic and anxiety. On 11Dec2011 the patient experienced a type of psychotic episode (not hospitalised) where he was agitated. The patient was one week and one day into the first pack. On (b) (6) 2011 the patient experienced another psychotic episode with two hours black out period, where did not remember anything of the two hours. He had become increasingly belligerent, agitated and psychotic. The police had to be called as he had threatened to burn his house with his wife and kids in inside. He had until this event a happy loving relationship with his wife and children. The patient also felt suicidal and had violent episodes. The psychotic reactions resulted in an apprehended violence order (AVO) being taken out against him by his wife subsequent to this event for six months. His marriage was in dire trouble. Two weeks after cessation of the varenicline tartrate he still felt highly anxious and panicky at times. None of this existed before the varenicline tartrate. The action taken in response to the events for varenicline tartrate was permanently withdrawn on an either (b) (6) 2011 or (b) (6) 2011. The patient came to see the pharmacist and returned the varenicline tartrate packs to the pharmacy on 10Jan2012. The pharmacist reported no psychotic episodes since the patient ceased varenicline tartrate. … The patient stopped smoking at the time of event onset. The patient had no personal history of emotional or mental health problems, homicidal/suicidal thoughts or attempts and it was unknown if the family did.

AER Number (b) (6)
A 38-year-old male patient started to receive oral varenicline (CHAMPIX) according to schedule as smoking cessation therapy in Aug2011, and until Nov2011. Shortly after starting with varenicline, he experienced reduced tolerance for alcohol. He had black outs even with small amounts. In addition he also experienced depression, libido decreased, personality change, sexual function decreased and irritability, all with onset in Aug2011. After varenicline was permanently discontinued in Nov2011, the events persisted. Outcomes were reported as not recovered. The Norwegian Medicines Agency assessed that there was an interaction between varenicline and alcohol. The causality between varenicline and alcohol and all the reported events was assessed as probable.

AER Number (b) (6)
A 49-year-old male patient of an unspecified ethnicity started to receive varenicline tartrate (CHAMPIX)…from an unspecified date at 1 mg at an unknown frequency for an unspecified indication. …On an unknown date, since being on varenicline for a month and a half, the patient experienced dry throat, stomachache, and alcohol tolerance lowered. He says that if he took a beer and a shot, he was disturbed as if he had taken 5 or 6 shots. The action taken with varenicline in response to the events, dry throat, stomachache, and alcohol tolerance lowered, was unknown.

AER Number (b) (6)
A 63-year-old female of an unspecified ethnicity started to receive oral varenicline tartrate (CHAMPIX) 1 mg on 03Jan2013 for smoking cessation therapy. …. On 07Jan2013, she experienced an overreaction to alcohol during the meal. Alcohol intake consisted of a glass of red wine. She took varenicline tartrate with food as indicated. Alcohol intolerance was not previously observed with varenicline treatment .There was no action taken with varenicline tartrate. The only action taken was to avoid alcohol during varenicline administration in the following days. The reaction with alcohol intake was not observed again during the meal along with varenicline. The consumer recovered from the event after 2-3 hours on the same day.

AER Number (b) (6)
This 33 year old female consumer states that on 12Aug2006 night she drank alcohol described as she was singing with the band so drank two and half glass white zinfandel and a watered down shot of Yukon to loosen her voice through the night in four hours. On 12Aug2006 after drinking the alcohol and taking Chantix (varenicline) she states that she had lost her memory described as she does not remember much from that night when she went to her car, described as except before when singing, described as did not remember calling her boyfriend, described as next thing she knows she woke up in a friend's house. She states that she did not slur her words, everything was fine, but she could not walk. She states that she has never lost her memory while being drunk before, so she thinks it is a interaction with alcohol and Chantix even though it is not listed in the information. On 13Aug2006 morning she started taking the 1mg Chantix and had a couple of cigarettes that day but states that the medicine is working. On 13Aug2006, last night she was anxious and could not sleep described as she fell asleep from 2300 and woke up at 0300 and did not sleep again until 0600, and she forced herself to go back to sleep for three more hours.

AER Number (b) (6)
This 47-year-old male patient reported that he started treatment with Champix (varenicline) on 29/Jun/2007 for smoking cessation. Currently patient is taken 1 mg twice a day. Patient refers that he drinks between 2 and 30 beers per day. Patient experienced 3 episodes of character change which lasted approximately 1-2 hours. The rest of the time patient tries to control himself but he is not totally normal. An interaction between varenicline and alcohol was suspected. In general this episode occurred with little alcohol but in one of them patient had drunk 10 beers. Patient was diagnosed of psychosis but this diagnosed was not performed directly with the patient since the patient did not want to visit neither a physician nor a psychologist or psychiatric specialist. No action was taken with varenicline in response to the event. Treatment with varenicline is still continuing.

AER Number (b) (6)
This 50-year-old female consumer reported she began treatment with Chantix (varenicline) starter pack as directed about a month ago in 2007 to quit smoking. ... She reported that after the 1st week she noticed after drinking alcohol that although she didn't feel drunk mentally, she was behaving very altered. She believed there was an interaction between Chantix and alcohol. She experienced gastrointestinal upset also described as feels like food was not digesting, nausea and couldn't sleep after starting the Chantix. She reported that she stopped drinking since being on Chantix, because her stomach was more upset (gastrointestinal upset) when she drank even with only 1 glass of wine. She also couldn't sleep and had more nausea more when she drank alcohol. She reported the Chantix works well for her.

AER Number (b) (6)
This 41-year-old female patient reported that she started treatment with Champix (varenicline) of unknown dose at approximately three months prior to reporting date for smoking cessation. On Champix she developed two episodes of a state in which she "could completely not remember some hours of the preceding evening" in connection with consumption of alcohol ("alt beer" (=top-fermented German dark beer), approximately one liter). This quantity of alcohol is "not unusual" for the patient. She drunk that quantitiy now and then distributed during the evening. There were no associated events. The outcome was reported as completely recovered. The patient has not smoked anymore for weeks.

AER Number (b) (6)
A physician reported his sister in law had been taking varenicline (CHAMPIX) for approximately 10 days when she experienced amnesia after an evening out
where she consumed 3 glasses of alcohol. The patient still did not remember what happened that evening. She has a history of breast cancer for which she has previously been taking NOLVADEX. At the
time of the adverse event she was not taking any other medication except calcium.
Follow-up (15Oct2008):
This physician further reported that this patient started varenicline (CHAMPIX) on 10Sep2008. On 20Sep2008, after intake of three glasses of alcohol, the patient experienced amnesia that lasted for about
eight hours. Before the onset of amnesia, the patient also experienced hot flushes. In the physician's opinion, the combined intake of and three glasses of alcohol are the cause of the adverse events.
Varenicline treatment had been interrupted due to the events and was still ongoing. The patient was in very good health.

AER Number (b) (6)
This consumer reported that her Caucasian male 39-year-old fiancé started taking varenicline (CHANTIX) on "12Oct2009", using the starter pack,
to stop smoking. Beginning on an unknown date, he drank one to two alcoholic beverages a night, for an unknown reason. The patient had the following relevant medical history: he was a recovering
alcoholic, who continued to drink alcohol but he controlled it by drinking about 1 to 2 alcoholic drinks a night; he was able to handle and tolerate alcohol very well, and 2 beers do not produce any signs of
impairment or changes in his mood or behavior; prior to varenicline, and when he would drink 1 beer no one could tell that he had any alcohol. The patient had no relevant concomitant medications or
relevant drug history. No personal of emotional or mental health problems. No patient history of trauma, surgery or disease that contributed to the events. The patient was smoking same amount at the time
of the onset of the events. The patient did not use any non-prescribed, illicit drugs at the time of the events. The patient drank one beer at the time of the events. The patient did not have any toxicology
screening performed at the time of the events. The patient had seen a mental health counselor during his divorce 6 years ago but he had not seen once since then. Relevant family history: his mother had
several mental breakdowns, she had severe depression, and she was hospitalized a couple of times due to the mental breakdowns. On 19Oct2009, the reporter noticed the following changes in his behavior
after he drank 1 beer: he was unable to tolerate the alcohol, he appeared to be extremely drunk l ke he was drinking non-stop for days, his speech was slurred, he was falling asleep in mid-sentence, and he
was stumbling and falling down. At the time of the onset of events the dose of varenicline was 0.5 mg twice daily. On 20Oct2009, the reporter called him and found out that he had 2 "Bloody Mary's" and the reporter explained that she considered this to be drinking alcohol excessively, because he was drinking alcohol at a bar during the day, which was completely unlike him and this was something he had not done since he has developed better control over his alcoholism; he had also been excessively tired, he had been talking in his sleep, and arguing with people in his sleep. On
20Oct2009, when he was drinking during the day when he was supposed to be at work, which required him to drive all day long, and when he came home that evening he appeared to be extremely drunk
and had the same events as he did the night before when he drank one beer. On 20Oct2009 and 21Oct2009, he forgot to take his evening doses of varenicline and instead he only took the morning dose on
these days. Alcohol was reported as an interacted drug. There was no relevant laboratory data, diagnosis, or treatment received. As of 22Oct2009, he continued taking varenicline, he had recovered from
missing the 2 evening doses, and all other events continue without improvement. It was unknown if the patient belonged to a smoking cessation support program.

AER Number (b) (6)
A female consumer started to receive varenicline (CHAMPIX) …film-coated tablet on 12Jan2010 for smoking cessation therapy. The patient had a relevant history of postpartum depression. Concomitant medications were not provided. For the first week she was not experiencing "nicfits" and was feeling calmer than usual. Approximately 8 days
later on 19Jan2010, when the patient moved onto the second week of treatment at the higher dose of 1 mg in the morning and 1 mg in the evening, the patient experienced what she could only describe as
agitation in her chest. Continuing this dose for two days, the patient stated that not only did the agitation not disperse; she now wanted to smoke. By the fifth day of the 1 mg dose, on 23Jan2010, she and her
partner attended a party at which she consumed alcohol consisting of 2 beers and 2 shooters over a 5 hour period. After the 1st beer and shooter, she became almost fully amnestic. Her partner told her that
he bought her another beer and shooter and that she seemed coherent even though she does not remember this part of the night.
She stated that she does not carry around feelings of suicide or feelings of
harm to others. She stated that she was not known to show such erratic behaviors as those shown on this night, which she descr bed as a psychotic episode. She ended up being
oblivious as to what went on the night before. The patient did not report any action taken with respect to varenicline nor specific outcomes of these events.

AER Number (b) (6)
This smoking cessation advisor reported that a male patient (age and race unknown) received varenicline tartrate (CHAMPIX) … On an unspecified date, the patient had a severe reaction after taking varenicline tartrate and consuming alcohol. It was reported that the patient passed out after consuming beer shandy with drunkenness. The reporter stated that this had happened twice to the patient. Alcohol was also considered a suspect medication. Relevant laboratory data was unknown.

AER Number (b) (6)
An unknown race and age female patient started to receive varenicline tartrate (CHAMPIX) 0.5mg twice a day for smoking cessation therapy on an unknown date. .. On an unknown date after the start of varenicline tartrate, the patient drank three bottles of beer and blacked out for a couple of hours. The patient reported that she could not remember anything about a great part of the evening.
It was like she experienced a kind of psychosis. The patient had the feeling that she was very drunk, she had fallen off the stairs but could not remember this and she had bruising all over the body.

AER Number (b) (6)
A male patient (age and race unknown) started to receive varenicline (CHANTIX) at an unknown dose and frequency to quit smoking since an unknown date. …. The patient reported that varenicline increased effect of the alcohol and he did not realize he was too drunk to drive on an unknown date.

AER Number (b) (6)
A 27-year-old Asian female patient received oral varenicline tartrate (CHAMPIX) of unknown dose from 01Oct2010 for smoking cessation therapy. …. On an unknown date, the patient experienced psychotic episode and alcohol interaction. It was reported that the patient experienced possibly 2 episodes while on treatment related to modest alcohol ingestion; two glasses white wine taken at same time. The action taken with varenicline tartrate in response to the events was unknown however a stop date of 19Nov2010 was also provided. The patient had recovered from the events at the time of the report. The reporter considered the events to be medically significant .

AER Number (b) (6)
This 53-year-old, White female consumer started to receive varenicline (CHANTIX) tablet orally since 5-6 weeks in 2011 at 0.5 mg daily for smoking cessation and also received sherry orally on 25Sep2011 (quantity unknown). The relevant medical history of the consumer included depression since an unknown date. The relevant concomitant medications of the consumer included escitalopram oxalate (LEXAPRO) tablet orally since an unknown date at 10 mg daily for depression. The consumer reported receiving sherry along with varenicline at a dose of 1 mg two times a day on 25Sep2011 after which she blacked out on 25Sep2011 which she suspected was due to a drug interaction between varenicline and sherry. There was no relevant laboratory data. The consumer was still continuing with the varenicline therapy at the time of the report but it was not known if she had received sherry after 25Sep2011.

AER Number (b) (6)
This currently 59-year-old, male patient (born in Jul1948) started varenicline tartrate (CHANTIX) since 02Jul2007 … to quit smoking … He started that day he did know there was as difference if he drank alcohol with it. On an unknown date (in 2007) whenever the patient drank beer while on varenicline therapy, he felt agitated and moody. So he didn't drink.

AER Number (b) (6)
A 52-year-old male patient of an unspecified ethnicity started to receive varenicline tartrate (CHAMPIX), orally on an unknown date … The patient took varenicline for one month. On an unknown date in the evening, the patient took the evening dose and had some alcohol and developed severe memory loss for that evening. He was not able to find his way home in his car. He discontinued varenicline on an unknown date and no further episodes. As of 01Mar2012, the outcome of memory loss was recovered.

AER Number (b) (6)
A 36 year-old female patient of unknown race received varenicline tartrate (CHAMPIX) of unknown dose from 06Feb2012 …. On 23Feb2012, the patient experienced abnormal behaviour. It was reported that the patient experienced affected behaviour when varenicline tartrate was taken with alcohol. The patient was reportedly doing okay on treatment but then drank alcohol and had very disturbed behaviour which settled upon stopping drug. Varenicline tartrate was permanently withdrawn on 23Feb2012 in response to the events and the patient recovered from the events on an unknown date.

AER Number (b) (6)
. A 31 year-old female patient of an unspecified ethnicity, started to receive varenicline tartrate (CHAMPIX) 1mg unit dose, orally, from 27Sep2012, for smoking cessation therapy. The patient was
also taking ethanol (ALCOHOL), details unspecified. .... On 06Oct2012, the patient experienced a behavioural change with ethanol with varenicline. She became aggressive. The patient
had no memory of the event and was informed by her husband. On 07Oct2012, varenicline tartrate was withdrawn. The action taken with ethanol is unknown. The patient recovered from the events on 08Oct2012.

AER Number (b) (6)
A 48 year old female consumer (initials (b) (6) started Champix (varenicline tartrate) on 25OCT2007. ... On 17NOV2007, likely in the first week of the first continuation pack, she complained she was not herself. After having 3 glasses of red wine, her behavior was completely inappropriate. She was loud, told her husband to shut-up and she said things she should not have said. The consumer used fowl language and threw wine at her husband. On 01DEC2007, she passed out described as blacked out. In response to these events, the consumer stopped taking Champix on 01DEC2007. This has upset
the consumer terribly, so she called Health Canada to report these events and they recommended she call Pfizer. The pharmacist was questioning an interaction with alcohol, specifically red wine. According
to the consumer, she drinks a glass of red wine every night with dinner. It was only after drinking 3 glasses of wine that she experienced these adverse events... The patient suffered depression descr bed as crying constantly for 2 to 3 days after she blacked out. In response to the events, Champix was discontinued on 01Dec2007. The patient recovered on 04Dec2007. No further information was provided

AER Number (b) (6)
A male patient, born in 1981, started to receive
varenicline tartrate (CHAMPIX) of unknown dose and frequency for an unknown indication on an unknown date for four weeks. Relevant medical history included attention deficit hyperactivity disorder
(ADHD). Relevant concomitant medication included dexamphetamine of unspecified dose taken six per day. The patient consumed a moderate amount of alcohol while on varenicline tartrate and
experienced amnesia. He experienced an incident where he had two drinks of alcohol the night before going to work. On arriving at work, he dropped all his possessions including a laptop, displayed bizarre
behaviour, threw papers around, and was taken to hospital. He had no memory of any of this. He lost his job as a result of the incident. He had also experienced dream-like states while on varenicline
tartrate. ...Varenicline tartrate was ceased immediately after the incident.

AER Number (b) (6)
This 44-year-old Caucasian female consumer reported starting varenicline (CHANTIX) on 07Mar2009, using the
starter pack to stop smoking. At the time of the onset of events the dose of varenicline was 0.5 mg daily. .... The patient does not drink alcohol often, but she does drink socially, which is about a couple of times a month and she works for a beer company so many times when she does work that requires social interaction she will drink
some beer, and she did not use any non-prescribed, or illicit drugs at the time of the event. ... In Mar2009, while she was still smoking cigarettes and taking varenicline the cigarettes tasted
different. On (b) (6) 2009, while attending a social function for work, she had drunk 3 beers over 3 hours, and she became completely agitated and she went into an aggressive state, because she was told
that she was loud, and she was asked to leave; after being asked to leave, she did leave and she exited the premises of where the incident occurred and while standing on the sidewalk outside of the
premises she was asked to leave again, but she felt that she had complied and she felt that the sidewalk was no one's property, so she began arguing with them when she was asked to leave the sidewalk,
she started screaming and yelling, she felt irritable, edgy, impatient, she did not feel like herself, and she did not feel quite normal, and she describes the feeling as being similar to premenstrual syndrome but
she had not been losing her temper, and due to these events she was arrested for trespassing and was placed in jail for 17 hours, after which she was exhausted. On (b) (6) 2009, she discontinued taking
varenicline after the evening dose due to the events on this date; the incident and events of 01Apr2009 are completely unlike her normal behavior, and it is something she had never done before.

AER Number (b) (6) 7
This follow-up report is being submitted to amend the classification of this case from serious and unexpected to serious and expected according to the USPI labeling, and also includes additional information.
This 45 year old male consumer reports that he was started on Chantix (varenicline) 0.5 mg once daily on 09Aug2006 to quit smoking. Around 10Aug2006, he had 3 glasses of wine and he became quite
drunk. Normally, he can drink 4 to 5 glasses of wine without trouble. He experienced hallucination, descr bed as seeing people who were not there. He suspects that there was an interaction between
Chantix and alcohol. Chantix dose was increased to 0.5 mg twice daily as planned. As of 15Aug2006, he is still taking Chantix. His quit date is tomorrow 16Aug2006 so he is still smoking.

AER Number (b) (6)
This consumer reports that her 63-year-old father started Chantix (varenicline) 0.5mg daily to progress to 1.0mg two times daily to stop smoking on 06Feb2007. He had no relevant medical history, relevant past drug history, or relevant concomitant medications. On 06Feb2007 he took his first dose of Chantix 0.5mg in the morning, and then later in the day on 06Feb2007 he was having cravings to smoke so he took another 0.5mg Chantix. On 06Feb2007, he drank a glass of wine with dinner and became nauseous, had a "small emesis", then had dizziness, slurred speech, and was "briefly unresponsive" descr bed as he was awake with his eyes open, but for a minute or two he did not answer when his wife spoke to him. On 06Feb2007, the being unresponsive quickly resolved, and the reporter stated her father said his mind was blank at that time. The reporter states his over-all behavior seemed like he was "extremely, extremely drunk" like he had way more than the 1 glass of wine that he actually had. The reporter took his blood pressure and he had a slightly elevated blood pressure at 146/86. At the time of the call, on 06Feb2007 the seeming drunk, dizziness and slurred speech were improving, he was responding when spoken to by family members, his mind was no longer blank, but he was still throwing up.

AER Number (b) (6)
This physician reports that this male patient (physician's husband; initials and age unknown) started therapy with Champix (varenicline) 1mg twice daily approximately two weeks prior to reporting date for nicotine withdrawal. Efficacy of Champix was very well (he smoked significantly less) and tolerance, too. However after consumption of usual quantities of alcohol (each time approximately two bottles of beer) he developed very distinct signs of drunkenness accompanied by coordination disorder and aggression. Interaction with alcohol was suspected because he developed the adverse event twice, each time shortly after intake of alcohol. The adverse event lasted approximately one hour. Each time the patient recovered. Due to the adverse event Champix was discontinued.
Follow-up (24May2007):
This same physician reported that the 38-year-old patient with hypertension and COPD started treatment with Champix 1x0.5mg/day on 09Apr2007. According to medical recommendation he took that dose of Champix until 11Apr2007. On 12Apr2007 Champix daily dose was increased to 2x0.5mg. After consumption of four bottles of beer on the same day he developed distinct signs of drunkenness accompanied by severe dizziness, giddiness, increased aggressivity and vomiting. The adverse event lasted two or three hours. From 16Apr2007 onwards he took Champix 1x2mg/day. After consumption of two bottles of beer on that day he developed again dizziness, giddiness and vomiting. The adverse event proceeded uncomplicatedly and was treated with repose. It persisted one or two hours, then resolved. The sudden start of a state of total drunkenness after consumption of a relatively small quantity of alcohol with, "amongst others", a behavior which was strange with respect to his personality (e.g. aggressivity) was remarkable. .. Due to the adverse event Champix was discontinued on 20Apr2007. The physician assessed a causal relationship of the adverse event and Champix was possible.
Follow-up (14Sep2007):
Additional information from the physician indicated that on Champix 1mg/day her husband developed pathologic inebriation and aggressively after the consumption of "two or three beers". Furthermore he was found to have increased liver function values which normalized again after four to six weeks.

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[i] **Kamens** HM, Andersen J, Picciotto MR. The nicotinic acetylcholine receptor partial agonist varenicline increases the ataxic and sedative-hypnotic effects of acute ethanol administration in C57BL/6J mice. **Alcohol** Clin Exp Res. **2010** Dec;34(12):2053-60.

[ii] Kaminski BJ and Weerts EM The Effects of Varenicline on Alcohol Seeking and Self-Administration in Baboons **Alcohol** Clin Exp Res **Volume 38, Issue 2, Feb 2014.**

[iii] Fucito LM, Toll BA, et al, A preliminary investigation of varenicline for heavy drinking smoker Psychopharmacology 2011 Jun;215(4):655-63

[iv] Childs E, Roche DJ, King AC, de Wit H. **Varenicline potentiates alcohol-induced negative subjective responses and offsets impaired eye movements.** Alcohol Clin Exp Res. 2012 May;36(5):906-14.

[v] McKee SA, Harrison EL, O'Malley SS, Krishnan-Sarin S, Shi J, Tetrault JM, Picciotto MR, Petrakis IL, Estevez N, Balchunas E. **Varenicline reduces alcohol self-administration in heavy-drinking smokers.** Biol Psychiatry. 2009 Jul 15;66(2):185-90.

[vi] Ginsburg BC, Lamb RJ. Effects of varenicline on ethanol- and food-maintained responding in a concurrent access procedure. Alcohol Clin Exp Res. 2013 Jul;37(7):1228-33

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/s/

CELIA J WINCHELL
07/29/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021928/S-032

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	September 18, 2014
To:	Sharon Hertz, MD Acting Director **Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** L. Shenee' Toombs, Pharm.D. Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	DMPP Concurrence with Submitted Medication Guide (MG)
Drug Name (established name):	CHANTIX (varenicline)
Dosage Form and Route:	Tablets
Application Type/Number:	NDA 21-928
Supplement Number:	S-032
Applicant:	Pfizer Inc.

1 INTRODUCTION

On October 24, 2013, Pfizer, Inc. submitted for the Agency's review a Prior Approval Supplement (PAS)-Efficacy to their approved New Drug Application (NDA) 21-928/S-032 for CHANTIX (varenicline) Tablets. The Applicant submitted S-032 in response to a PAS Request/Risk Evaluation and Mitigation Strategy (REMS) Modification Notification Letter from the Division of Analgesia, Anesthesia, and Addiction products (DAAAP) dated September 4, 2013. In the letter, DAAAP notified Pfizer, Inc. of the need to revise their currently approved Medication Guide, based on review of the applicant's 18-month Risk Evaluation and Mitigation Strategy (REMS) assessment submission (dated October 17, 2012), to facilitate the goal of informing patients about neuropsychiatric events of CHANTIX. In their cover letter for S-032, the Applicant references an information request email received on May 24, 2013, regarding review of data pertaining to the concomitant use of CHANTIX and alcohol, and their submission dated August 14, 2013 containing these requested data. The Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) completed a collaborative review of the Applicant's proposed Medication Guide (MG) for S-032 on July 17, 2014.

On August 6, 2014, DAAAP issued a Safety Labeling Change Notification/REMS Modification Notification letter to the Applicant. The letter requested that the Applicant submit a labeling supplement for specific required changes to the approved CHANTIX Prescribing Information (PI) and corresponding changes to the MG. On September 3, 2014, the Applicant submitted PAS 038. This supplement provides the Applicant's proposed labeling revisions in response to the Safety Labeling Change Notification/REMS Modification Notification letter issued on August 6, 2014.

This memorandum documents the DMPP and OPDP review and concurrence with the Applicant's proposed Medication Guide (MG), as revised by the Agency and Pfizer, Inc. during a teleconference held on September 16, 2014. On September 17, 2014, the Applicant submitted updated labeling by email, based on agreements reached during the teleconference.

The REMS is being reviewed by the Division of Risk Management (DRISK) and will be provided to DAAAP under separate cover.

2 MATERIAL REVIEWED

- Draft CHANTIX (varenicline) Tablets MG received on September 3, 2014, and further revised by the review team on September 10, 2014.
- Draft CHANTIX (varenicline) Tablets MG received on September 17, 2014.
- Draft CHANTIX (varenicline) Tablets Prescribing Information (PI) received on September 3, 2014, and revised by the review team on September 10, 2014.

- Draft CHANTIX (varenicline) Tablets Prescribing Information (PI) received on September 17, 2014.
- CHANTIX (varenicline) Tablets Safety Labeling Change Notification/REMS Modification Notification letter issued on August 6, 2014.
- DMPP-OPDP Review of CHANTIX (varenicline) Tablets Patient Labeling (Medication Guide), dated July 17, 2014.

3 CONCLUSIONS

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.

4 RECOMMENDATIONS

- Consult DMPP and OPDP regarding any additional revisions made to the Prescribing Information (PI) to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

SHARON R MILLS
09/18/2014

SAMUEL M SKARIAH on behalf of LATOYA S TOOMBS
09/18/2014

BARBARA A FULLER
09/18/2014

LASHAWN M GRIFFITHS
09/18/2014

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

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/s/

AYANNA S AUGUSTUS
09/18/2014

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Consumer Drug Promotion (DCDP)

****Pre-decisional Agency Information****

Memorandum

Date: July 18, 2014

To: Ayanna Augustus, Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

From: L. Shenee Toombs, Regulatory Review Officer, (OPDP)

CC: Olga Salis, Senior Regulatory Health Project Manager (OPDP)
Michael Wade, Regulatory Health Project Manager (OPDP)

Subject: NDA 021928
OPDP labeling comments for CHANTIX® (varenicline) Tablets
Labeling Review

OPDP has reviewed the proposed package insert (PI) and Medication Guide (Med Guide) for CHANTIX® (varenicline) Tablets (Chantix) that was submitted for consult on November 1, 2013. Comments on the proposed PI are based on the version sent via email from Ayanna Augustus (RPM) on July 2, 2014 entitled "Draft Chantix PI and MG_S032 07 01 14.doc"

Comments regarding the PI are provided on the marked version below.

Please note that comments on the Medication Guide will be provided under separate cover as a collaborative review between OPDP and the Division of Medical Policy Programs (DMPP).

Thank you for the opportunity to comment on these proposed materials.

If you have any questions, please contact Shenee' Toombs at (301) 796-4174 or latoya.toombs@fda.hhs.gov.

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/s/

LATOYA S TOOMBS
07/18/2014

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	July 17, 2014
To:	Bob A. Rappaport, MD Director **Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** L. Shenee' Toombs, Pharm.D. Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	CHANTIX (varenicline)
Dosage Form and Route:	Tablets
Application Type/Number:	NDA 21-928
Supplement Number:	S-032
Applicant:	Pfizer Inc.

1 INTRODUCTION

On October 24, 2013, Pfizer Inc. submitted for the Agency's review a Prior Approval Supplement (PAS)-Efficacy to their approved New Drug Application (NDA) 21-928/S-032 for CHANTIX (varenicline) Tablets. The Applicant submitted S-032 in response to a PAS Request/Risk Evaluation and Mitigation Strategy (REMS) Modification Notification letter from the Division of Analgesia, Anesthesia, and Addiction Products (DAAAP) dated September 4, 2013. In the letter, DAAAP notified Pfizer Inc. of the need to revise their currently approved Medication Guide, based on review of the Applicant's 18-month Risk Evaluation and Mitigation Strategy (REMS) assessment submission (dated October 17, 2012), to facilitate the goal of informing patients about Neuropsychiatric events of Chantix. In their cover letter for S-032, the Applicant references an Information Request email received on May 24, 2013, regarding review of data pertaining to the concomitant use of CHANTIX and alcohol, and their submission dated August 14, 2013 containing these requested data.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) on November 1, 2013 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG).

The Risk Evaluation and Mitigation Strategy (REMS) is being reviewed by the Division of Risk Management (DRISK) and will be provided to DAAAP under separate cover.

2 MATERIAL REVIEWED

- Draft CHANTIX (varenicline) Tablets MG received on October 24, 2013, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 2, 2014.
- Draft CHANTIX (varenicline) Tablets Prescribing Information (PI) received on October 24, 2013, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 2, 2014.
- Prior Approval Supplement Request/REMS Modification Notification letter dated September 4, 2013.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication*

Information for People with Vision Loss. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 11.

In our collaborative review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured consistency with the Medication Guide attached to the Prior Approval Supplement Request/REMS Modification Notification letter dated September 4, 2013.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

SHARON R MILLS
07/17/2014

LATOYA S TOOMBS
07/17/2014

LASHAWN M GRIFFITHS
07/17/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021928/S-032

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-032

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 021928/S-032

ACKNOWLEDGEMENT --
PRIOR APPROVAL SUPPLEMENT

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

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

Dear Dr. Donohew:

We have received your Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 021928

SUPPLEMENT NUMBER: 032

PRODUCT NAME: Chantix (varenicline) Tablets; 0.5 mg and 1 mg

DATE OF SUBMISSION: October 24, 2013

DATE OF RECEIPT: October 24, 2013

This supplemental application proposes revisions to the **DRUG INTERACTIONS** section of the Package Insert and Medication Guide. Information regarding potential interaction between alcohol and varenicline is added.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on **December 23, 2013**, in accordance with 21 CFR 314.101(a). If the application is filed, the goal date will be April 24, 2014.

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3).

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia, and Addiction Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have questions, contact me at ayanna.augustus@fda.hhs.gov or (301) 796-3980.

Sincerely,

{See appended electronic signature page}

Ayanna Augustus, Ph.D., R.A.C.
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

AYANNA S AUGUSTUS
10/31/2013