CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

021928Orig1s036

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-036

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021928/S-036

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-036

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

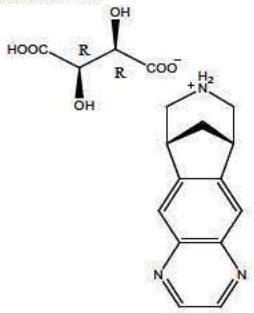
In case of overdose, standard supportive measures should be instituted as required.

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

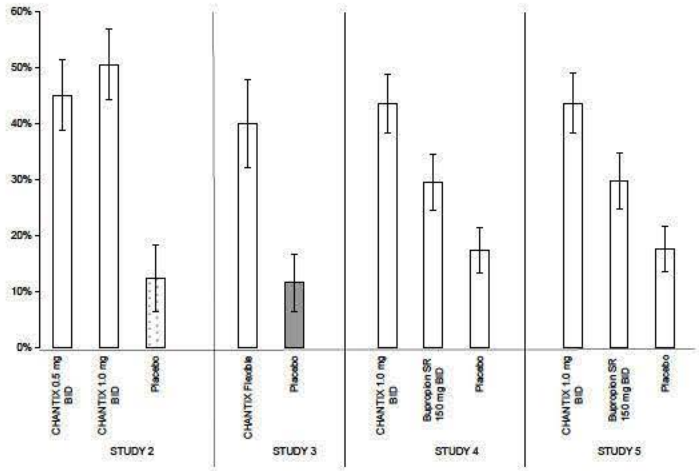


Table 6: Continuous Abstinence, Weeks 9 through 12 (95% confidence interval)

	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

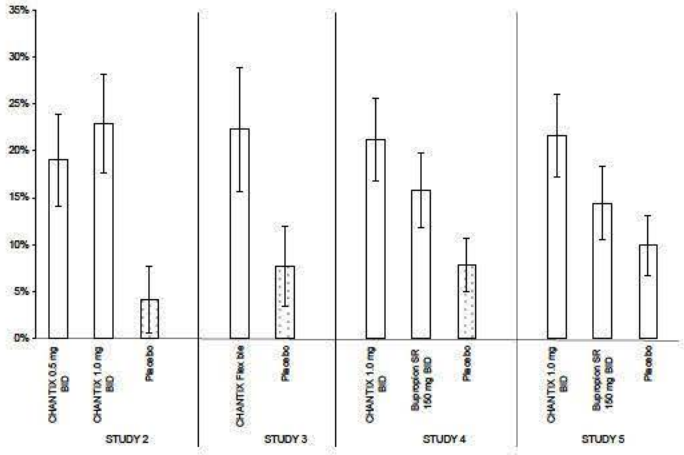


Table 7: Continuous Abstinence, Weeks 9 through 52 (95% confidence interval) across different studies

	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%)

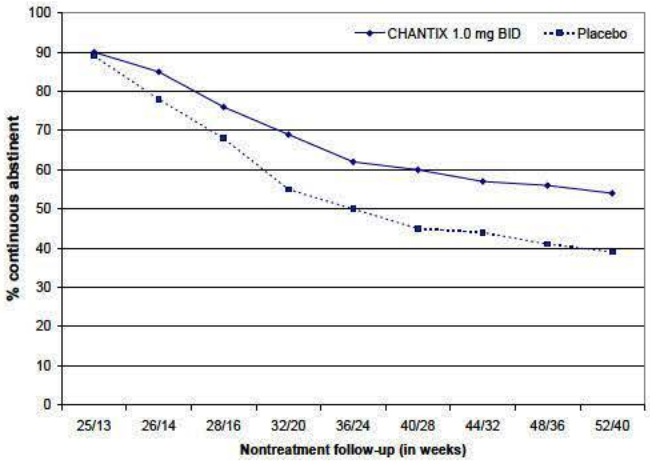
BID = twice daily

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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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021928/S-036

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.

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-036

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	9/19/14
From	Judith A. Racoosin, MD, MPH
Subject	Serious neuropsychiatric events
NDA # **Supplement#**	21-928 S-036
Applicant	Pfizer
Date of Submission	4/8/2014
Relevant reviews	DEPI II review: 9/18/14 DB VII – 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

Varenicline, a partial α4β2 acetylcholine nicotinic receptor agonist, was approved in May 2006 in the United States "as an aid to smoking cessation treatment." Varenicline's approval was based on six placebo- and active-controlled trials of 6 to 12 weeks duration in over 3500 chronic cigarette smokers (average 21 cigarettes per day and average smoking history of 25 years).

Varenicline's original approved labeling included a listing of the following neuropsychiatric events in the ADVERSE REACTIONS section: insomnia, abnormal dreams, and nightmares. As information about serious neuropsychiatric events emerged in the postmarket period, the varenicline labeling evolved to incorporate this information:

- January 2008: Based on data from spontaneous postmarket reports of serious neuropsychiatric events, FDA determined that varenicline was associated with serious neuropsychiatric events including suicidal ideation, suicidal behavior, changes in behavior, agitation, depressed mood, and worsening of preexisting psychiatric illness. A new warning was added to the WARNINGS section describing these serious neuropsychiatric events; and recommendations were added for patients, their families, and caregivers to monitor for these serious neuropsychiatric events during varenicline treatment.

- May 2008: FDA utilized two postmarket safety authorities acquired under the FDA Amendments Act of 2007. FDA required Pfizer to implement a Risk Evaluation and Mitigation Strategy (REMS) to ensure that the benefits of varenicline as an aid to smoking cessation outweighed its risk of serious neuropsychiatric events. The REMS required a Medication Guide to ensure varenicline-

treated patients are aware of the risk of serious neuropsychiatric events. Additionally, FDA issued a postmarket requirement (PMR) to Pfizer to conduct a randomized controlled trial to assess the risk of serious neuropsychiatric events with varenicline.

- July 2009: A BOXED WARNING section was added to the varenicline labeling that described information already included in the WARNINGS section concerning the serious neuropsychiatric events and recommendations to patients and their caregivers to discontinue varenicline if these serious neuropsychiatric events occurred. Furthermore, the WARNINGS section was updated to include additional varenicline-associated serious neuropsychiatric events including hostility, mania, psychosis, hallucinations, and paranoia.

On April 8, 2014, Pfizer submitted the labeling supplement reviewed herein (Chantix, NDA 21-928, S-036) proposing changes to the varenicline labeling relating to the risk of serious neuropsychiatric events. In the cover letter of this supplement, Pfizer asserts that, "…since 2009, more reliable data on the NPS [neuropsychiatric] safety of Chantix have become available, including meta-analyses of placebo-controlled clinical trials and data from observational studies comparing varenicline to other smoking cessation pharmacotherapies. As presented in this submission, these data (b) (4)

Based on Pfizer-conducted meta-analyses of randomized controlled trials of varenicline and a Pfizer-conducted review of five publications of observational studies of patients treated with varenicline compared to patients treated with nicotine replacement therapy (NRT) or bupropion, Pfizer proposed the following major changes to the varenicline labeling:

- (b) (4)
- WARNINGS AND PRECAUTIONS section of the FPI
    - In section 5.1 WARNINGS AND PRECAUTIONS / Neuropsychiatric Symptoms and Suicidality, add information from neuropsychiatric meta-analyses of clinical trial data and observational studies

In addition to presenting conclusions drawn from the meta-analyses conducted and the observational studies reviewed, Pfizer (b) (4)

(b) (4)

Prior to addressing the contents of Pfizer's submission, this review describes the regulatory history of the serious neuropsychiatric events issue to provide context for interpreting the labeling changes proposed by the sponsor. Because the sponsor (b) (4)

Regulatory History

Varenicline is a partial α4β2 acetylcholine nicotinic receptor agonist approved in May 2006 as an aid to smoking cessation. The treatment regimen is 1 mg twice daily for 12 weeks (with an initial one-week titration). A second 12-week course may be taken to increase the chance of maintenance of abstinence.

In May 2007, the European Medicines Agency (EMA- previously, EMEA) informed FDA that they were investigating a signal of suicidality-related adverse events. A chronology of the subsequent regulatory actions and public communications that followed is shown below.

May 2006	NDA approval for varenicline in the U.S. (trade name "Chantix")
September 2006	Approval in the European Union (trade name "Champix")
May 2007	European Medicines Agency informed FDA that they were investigating a signal of suicidal-related events with varenicline and had asked Pfizer to submit a postmarket suicidal-event analysis.
Nov 2007	Information added to ADVERSE REACTIONS section of labeling; Early communication of an ongoing safety review
Jan 2008	Serious neuropsychiatric events information upgraded to the WARNINGS AND PRECAUTIONS section of the labeling
Feb 2008	Public health advisory issued

April 2008	Center Director briefing concerning varenicline and serious neuropsychiatric events: discussed the benefits of varenicline to help patients achieve smoking cessation vs. the risk of serious neuropsychiatric events
May 2008	Added MedGuide-only REMS; issued a postmarket required study/ clinical trial; Updated public health advisory; FAA bans use of varenicline by pilots and air traffic controllers
July 2009	Added BOXED WARNING section to varenicline and bupropion labeling; Public health advisory issued regarding addition of boxed warning to both varenicline and bupropion
Oct 2011	Drug Safety Communication issued reporting the results of two FDA-sponsored epidemiology studies that evaluated the risk of serious neuropsychiatric events associated with varenicline

AERS Reviews- 2008

Prior to the addition of the boxed warning for serious neuropsychiatric events, the Division of Adverse Event Analysis II[1] completed two reviews of AERS[2] cases- one focused on suicidality events (finalized July 2008) and the other focused on neuropsychiatric events not related to suicidality (finalized Dec 2008).

Briefly, the review of suicidality events showed that from initial marketing through November 2007, AERS had 262 cases of suicidal-related events for the smoking cessation drugs (varenicline, n=153; bupropion[3], n=75; transdermal nicotine, n=34). Varenicline had a higher proportion of cases for suicidal ideation (76%) vs. bupropion (61%) or nicotine (47%) and a lower proportion of suicide (attempt and completed) or other self-injurious behavior (24%) than the other drugs (bupropion 39%; transdermal nicotine 53%). Median time to event was 8-14 days.

[1] The Division of Adverse Event Analysis II is now called the "Division of Pharmacovigilance II".
[2] The FDA Adverse Events Reporting System was called "Adverse Event Reporting System (AERS)" at the time these review were done.
[3] Bupropion was approved for the treatment of depression as Wellbutrin about a decade before it was approved as Zyban for smoking cessation. In order to limit the review to those exposed to bupropion for the treatment of smoking cessation, included cases had to either reference bupropion by the trade name Zyban, or mention the indication of smoking cessation in the report.

Varenicline had the largest proportion of reports (24%) in which it was explicitly stated that the suicidal event(s) were a first-time significant behavior change from the past, followed by bupropion (15%) and nicotine (none). Varenicline cases had the most reports that described pre-existing disease worsening (17%) compared to nicotine (12%) and bupropion (8%); depression was the most common pre-existing psychiatric condition that worsened for all three drugs. The overall conclusion was that AERS data suggested a possible association between suicidal events and the use of varenicline and bupropion, given that there were postmarket cases of positive dechallenge and a few positive rechallenges, a close temporal relationship between the event and drug use, and the occurrence of suicidal events in patients without any psychiatric history.

A recommendation was made to add a BOXED WARNING section to highlight the risk of serious neuropsychiatric events and to request a PMR to determine the incidence of serious neuropsychiatric event with varenicline, especially in patients with preexisting psychiatric disorders. For Zyban (bupropion), which was included as a comparator in this review, there was a similar recommendation to add language to the already existing BOXED WARNING section about the risk of suicidality in those using bupropion for smoking cessation.

A review of AERS cases describing neuropsychiatric events other than suicidality was completed in December 2008. Because of the increased awareness that there was "stimulated" reporting[4] starting in September 2007, this review was conducted from market approval through August 2007. Additionally, because there were few evaluable cases reported with nicotine replacement therapies (NRT), NRT was not used as a comparator in this review.

For both varenicline and bupropion, anxiety and depression were the two most commonly reported events. For both drugs, ~20% of the cases reported psychosis/mania or aggression-events. For varenicline, the most common event for the psychosis/mania and aggression groups was *hallucination* and *aggression* respectively; for bupropion it was *paranoia* and *hostility* respectively. There was a temporal association between the two drugs and all groups of events with a median onset time between three and seven days. Positive dechallenge was reported in 33% and 63% of the varenicline and bupropion cases respectively.

[4]Stimulated reporting is an increase in adverse event reporting that often occurs following any risk communication or media attention to a particular safety issue due to enhanced awareness.

For all event groups, patients with no reported psychiatric history ranged from 17 to 33% for varenicline and 13 to 30% for bupropion. For all event groups, patients with no reported concomitant psychiatric medications ranged from 4 % to 13% for varenicline and 0 to 25% for bupropion. There were more cases with varenicline (29-33%) that reported a behavioral change from the patient's past (i.e., either new experience or disease worsening) than with bupropion (0-9%).

More varenicline patients (27%-53%) had a history of psychiatric disease than bupropion (0%-20%); however, there was a portion of the bupropion population for which unknown medical history was very high (78%). The most commonly reported psychiatric history across the case series was depression and bipolar disorder. Psychiatric medication use ranged from 13 to 73% for varenicline and 21% to 70% for bupropion.

The recommendations included enhancements to the proposed BOXED WARNING section and other parts of labeling to warn of the risk of these other neuropsychiatric events.

Dr. Celia Winchell, Medical Team Leader for Addiction Products, stated in her memo to the file dated 12/12/08, the following rationale for a BOXED WARNING section for varenicline and bupropion, "The need for a boxed warning was discussed extensively at the highest levels of Center management and it was determined that the events met criteria for placement in a boxed warning. Specifically, the events are of a serious nature and have adverse consequences that can be prevented by close monitoring."

Risk Evaluation and Mitigation Strategy (REMS)/ Postmarket Requirement (PMR) Clinical Trial

As the understanding of the serious neuropsychiatric events with varenicline evolved, it was determined that a REMS was necessary to ensure that the benefits of varenicline outweighed the risks. The May 16, 2008 letter that required the REMS also included issuance of a postmarket requirement (PMR) for a clinical study or trial to assess the known serious risk of neuropsychiatric events, including changes in behavior, agitation, depressed mood, and suicidal thoughts or actions. The clinical study or trial was being required because it was determined that neither an analysis of spontaneous postmarket adverse events reported under subsection 505(k)(1) of the FDCA nor the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA would be sufficient to assess the known serious risk of neuropsychiatric events, including changes in behavior, agitation, depressed mood, and suicidal thoughts or actions related to the use of varenicline products. A similar REMS and PMR was required of another smoking cessation product, bupropion (Zyban).

After internal discussion and discussion with Pfizer and GlaxoSmithKline (sponsor of bupropion), further guidance on the PMR was issued in a letter dated June 2, 2009. As seen in the description below, FDA determined that a randomized controlled clinical trial would be required to meet the PMR goals:

> A large randomized, double-blind, active- and placebo-controlled trial to compare the risk of clinically significant neuropsychiatric events, including but not limited to suicidality, in individuals using varenicline, bupropion, nicotine replacement therapy, or placebo as aids to smoking cessation over 12 weeks of treatment, and to determine whether individuals with prior history of psychiatric disorders are at greater risk for development of clinically significant neuropsychiatric events compared to individuals without prior history of psychiatric disorders while using varenicline as an aid to smoking cessation. The study should be sufficiently powered to adequately assess clinically significant neuropsychiatric events with each treatment and in both of the two subgroups (i.e., with and without psychiatric disorders).

After continued discussions internally and with the sponsors, the PMR protocol was found acceptable around July 2010 for the protocol and the statistical analysis plan). In recognition of the variable and ill-defined nature of the neuropsychiatric events reported, and the difficulty of capturing such events in traditional MedDRA coding[5], a composite endpoint was developed specifically for the PMR trial and instruments to solicit relevant events were included in the trial procedures. The primary safety endpoint is the occurrence of at least one treatment-emergent "severe" adverse event of anxiety, depression, feeling abnormal, or hostility or the occurrence of at least one treatment emergent "moderate" or "severe" adverse event of: agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal ideation, suicidal behavior, or completed suicide.

Two interim analyses were planned for the RCT, the first after half of the patients completed 20 weeks of the trial, and the second when 75% of patients completed the trial to that point. Pfizer's description of the first interim analysis (submitted October 29, 2013) follows below:

> IA1 was designed to assess data on the first 4,000 subjects (50% enrollment)

[5] MedDRA (Medical Dictionary for Regulatory Activities) is an international standardized lexicon of medical terms used to code adverse events. MedDRA was developed by the ICH (International Conference of Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) and released in 1999. MedDRA contains about 21,000 different preferred terms (PTs, e.g., nausea, hypotension) for various adverse events. These PTs are vertically grouped into 3 levels. The highest level for a PT is the System Organ Class, of which there are 26 (e.g., Cardiac disorders, Infections and infestations). http://www meddra.org/sites/default/files/guidance/file/intguide_17_1_english.pdf

randomized into the study (please refer to Section 2 of the interim analysis plan). The second interim analysis is planned for the first 6,000 subjects randomized (75% enrollment).

The IA1 database snapshot occurred on 5 August 2013 after all IA1 subjects had either completed the Week 20 visit or had discontinued from the study prior to the Week 20 visit. The Week 20 visit was the first scheduled in-clinic visit after the treatment-emergent period (the basis of the primary study endpoint). Of the 4,001 randomized subjects captured in this snapshot, 3,921 also had data confirming at least one dose of study drug. The remaining subjects either did not receive study drug or had missing data for study drug dosing.

The results of this blinded, pooled 50% interim analysis were completed and provided to the unblinded statistician for the IDMC on 12 September 2013. The rate of the primary neuropsychiatric event endpoint was 3.98% (156/3,921). This exceeded the 3.5% threshold specified in the protocol.

As a result, the study will continue enrollment as planned until the results of the second planned interim analysis (IA2) become available. IA2 will be conducted 20 weeks after 6,000 (75%) of the subjects have been randomized.

Pfizer's description of the second interim analysis (submitted June 10, 2014) follows below:

IA2 was planned to include data from the first 75% (6,000) subjects randomized into the study. The IA2 database snapshot occurred on 24 April 2014 after all IA2 subjects had either completed the Week 20 visit or had discontinued from the study prior to the Week 20 visit. The Week 20 visit was the first scheduled in-clinic visit after the treatment-emergent period (the basis of the primary study endpoint).This snapshot included 6,005 subjects.

The results of this pooled 75% interim analysis were completed and provided to the Independent Data Monitoring Committee (IDMC) on 19 May 2014. In addition to their standard safety review, the IDMC reviewed actual and projected neuropsychiatric adverse event rates for each of the 4 treatment arms in both the neuropsychiatric and the non-neuropsychiatric cohorts and the total population to establish if the planned sample size of 8,000 was sufficient. Their recommendation was to continue the study to the target enrollment of 8,000 as specified in the protocol. The blinded rate of the primary neuropsychiatric adverse event endpoint in the total population was 4.5% (268/6005).

In July 2014, FDA was informed by Pfizer that the RCT completed enrollment, and that the final study report is expected to be submitted in the third quarter of 2015.

Regulatory Requirements and Guidance Recommendations for the BOXED WARNING Section and Other Relevant Sections of the Labeling[6]

A familiarity with the pertinent regulatory requirements and guidance recommendations of the prescribing information is useful for determining 1) If the meta-analyses and observational study data about the risk of serious neuropsychiatric events (b) (4) in the varenicline labeling; and 2) How the risk information about serious neuropsychiatric events should be communicated in the varenicline labeling.

Prescribing Information

The prescribing information is written for healthcare providers and must:[7]

- Contain a summary of the essential scientific information needed for the safe and effective use of the drug,
- Be informative and accurate and neither promotional in tone nor false or misleading in any particular, and
- Be updated when new information becomes available that causes the labeling to become inaccurate, false, or misleading.

Adverse Reactions

For the purposes of prescription drug labeling, an adverse reaction (AR) is an undesirable effect reasonably associated with the use of the drug. This definition does not include all adverse events observed during use of a drug, only those for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event.[8]

Boxed Warning

The BOXED WARNING section of the labeling must be the first section in the FULL PRESCRIBING INFORMATION, must be surrounded by a "box" (i.e., a single black line), and must contain

[6] This section of the review was provided by Eric Brodsky, MD, of OND's Study Endpoints and Labeling Development Team, and is excerpted from the briefing document for the October 16, 2014 advisory committee meeting.
[7] See 21 CFR 201.56(a)
[8] See 21 CFR 201.57(c)(7)

"contraindications or serious warnings, particularly those that may lead to death or serious injury."[9] This section must briefly explain the clinically significant adverse reaction or risk and refer to more detailed information in the CONTRAINDICATIONS or WARNINGS AND PRECAUTIONS sections. A boxed warning is ordinarily used to highlight for prescribers one of the following situations:[10]

- There is an AR so *serious*[11] in proportion to the potential benefit from the drug (e.g., a fatal, life-threatening or permanently disabling AR) that it is essential that it be considered in assessing the risks and benefits of using a drug;
- There is a serious AR[7] that can be prevented or reduced in frequency or severity by appropriate use of the drug (e.g., patient selection, careful monitoring, avoiding certain concomitant therapy, addition of another drug or managing patients in a specific manner, avoiding use in a specific clinical situation); or
- FDA approved the drug with restrictions to assure safe use because FDA concluded that the drug can be safely used only if distribution or use is restricted [e.g., certain Elements to Assure Safe Use (ETASU) under Risk Evaluation and Mitigation Strategies (REMS)].

A boxed warning can also be used in other situations:[8]

- To highlight a warning that is especially important to the prescriber.
- For a drug that poses risk-benefit considerations that are unique among drugs in a drug class (e.g., when the drug is the only one in its class to have a particular clinically significant AR or risk and is indicated as a second line therapy because of that clinically significant AR or risk).

Boxed warnings are more likely to be based on observed serious AR, but there are instances when a boxed warning based on an expected AR would be appropriate. For example, an Embryofetal Toxicity boxed warning would be appropriate for a drug based on evidence in humans or animals that drugs in its pharmacologic class pose a serious risk of developmental toxicity during pregnancy, even though no AR was seen with the drug.[8]

Removal of a Boxed Warning

There is no specific regulation or guidance that has established criteria to remove a Boxed Warning. However, if the criteria[8] for including a boxed warning are no longer met, it is reasonable to remove it.

Warnings and Precautions

The WARNINGS AND PRECAUTIONS section should describe serious or clinically significant AR that have occurred with the drug or risks that are expected to occur (e.g., based on the drug class; animal data

[9] See 21 CFR 201.57(c)(1)
[10] See the *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling* guidance
[11] For the purposes of prescription drug labeling, a *serious AR* is an AR that results in the following outcomes: Death, life-threatening AR, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly or birth defect. Furthermore, AR may be considered serious if they jeopardize the patient and require medical or surgical intervention to prevent one of the outcomes listed in this definition. See the *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling* guidance.

raise substantial concern about the potential occurrence of the AR in humans). 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."[12] The following factors can be used in determining if AR are clinically significant:[8]

- The relative seriousness of the disease or condition being treated.
  - Non-serious AR caused by drugs intended to treat minor, self-limiting conditions may be considered clinically significant.
  - However, those same AR caused by drugs intended to treat serious or life-threatening conditions (e.g., malignancies) may be considered much less clinically significant and not appropriate for inclusion in this section.
- A high absolute risk or rate of AR occurrence
- An AR that may lead to a potentially serious outcome unless an action is taken (e.g., dosage reduction or discontinuation) to prevent a serious outcome
- An AR that could be prevented or managed with appropriate patient selection, monitoring, or avoidance of concomitant therapy.
- An AR that can significant affect patient compliance particularly when non-compliance has potentially serious consequences.

Each WARNINGS AND PRECAUTIONS subsection should include a succinct description of a topic and should contain the following (if known):[8,11]

- A succinct description of the serious or clinically significant AR or risk
- Known risk factors for the AR
- Outcome
- Numerical estimate of the risk or AR rate
- Steps to take to prevent, mitigate, monitor, or manage the AR

Contraindications

The CONTRAINDICATIONS section must describe situations in which the drug should not be used because the risk of use (e.g., certain potentially fatal AR) clearly outweighs any possible therapeutic benefit. These situations include the use of the drug in a subpopulation of patients that have a substantial risk of being harmed by the drug and for whom no potential benefit makes the risk acceptable. Known hazards and not theoretical possibilities must be listed.[13] Contraindications may be based on:[8]

- Observed AR
- Anticipated AR supported by data (e.g., pharmacology, chemistry, or drug class data; or animal data) and the likelihood ad severity of the AR

[12] See 21 CFR 201.57(c)(6)
[13] See 21 CFR 201.57(c)(5)

Contents of Pfizer's submission

Division of Epidemiology II summary of observational studies examining the relationship between varenicline and neuropsychiatric adverse events[14]

The sponsor identified five observational studies of varenicline-associated neuropsychiatric risk (four publications and one unpublished study), including three which examined the association between Chantix and risk of neuropsychiatric medical encounters (i.e., hospitalizations, emergency room visits, and outpatient visits) and two which investigated the association between Chantix and risk of suicide, non-fatal self-harm, and initiation of an antidepressant (as a proxy of incident depression). One of the studies (Thomas et al) was an expansion of an earlier study (Gunnell et al).[15]

All the reviewed observational studies were based on population-level data reflecting the real-world smoking cessation product user population. Their inclusion of patients with a history of neuropsychiatric disorders extends the generalizability of the findings, because that population was excluded in most clinical trials conducted to date. The studies also all attempted to control for confounding by employing appropriate design and analytical approaches. Please see Table 1 for a summary of main study findings of the reviewed observational studies.

[14] This summary was prepared by the Division of Epidemiology II (DEPI-II) for inclusion in the briefing document for the Chantix Advisory Committee scheduled for October 16, 2014. The reader is referred to DEPI-II's full review of the S-036 labeling supplement (dated 9/18/14) for a summary of each reviewed study.

[15] Both Thomas et al and Gunnel et al studies were based on the same source data (CPRD) with overlapping time-frames, but Thomas et al included a longer time-frame and linked to two other data sources to enhance outcome ascertainment

Table 1. Main study findings of the observational studies on varenicline and risk for neuropsychiatric events

Study	Outcome	Analyses	Varenicline (N event/ Total/IR*)	Reference group		Fully-adjusted Hazard Ratio
				NRT (N event /total/IR*)	Bupropion (N event/ total/IR*)	
Meyer et al. 2013	NPS hospitalization (primary diagnosis) in 30 days	New users, PS-matched	16/10,814/18	14/10,814/16	-	1.14 (0.56-2.34)
Meyer et al. 2013	NPS hospitalization (any diagnosis) in 30 days	New users, PS-matched	34/10,710/39	43/10710/49	-	0.79 (0.50-1.24)
Meyer et al. 2013	NPS Outpatients visits in 30 days	New users, PS-matched	234/10710/269	327/10710/378	-	0.71 (0.60-0.84)
VA study Unpublished	NPS hospitalization (primary diagnosis) in 30 days	New users, PS-matched	16/14,131/16	21/14,131/21	-	0.76 (0.40-1.46)
VA study Unpublished	NPS hospitalization (primary diagnosis) in 30 days	Prevalent users, PS-matched	29/12,258/29	94/24,185/47	-	0.74 (0.49-1.14)
Pasternak et al,2013	NPS emergency room visit or hospitalization in 30 days	New users, PS-matched	39/17,975/27	-	46/17,935/31	0.85 (0.55-1.30)
Gunnell et al. 2009	Suicide or non-fatal self-harm in 90 days	Prevalent users	18/10,973/5.3*	141/63,265/7.5*	-	1.12† (0.67-1.88)
Gunnell et al. 2009	Suicide thoughts in 90 days	Prevalent users	5/10,973/NA	30/63,265/NA	-	1.43† (0.53-3.85)
Thomas et al. 2013	Suicide or non-fatal self-harm in 90 days	New users	19/30,352/3	69/78,407/4	-	0.88[&] (0.52-1.49)

Gunnell et al. 2009	Initiation of antidepressants in 90 days‡	Prevalent users	292/9162/NA	1792/49415/NA	-	0.88† (0.77-1.00)
Thomas et al. 2013	Initiation of antidepressants in 90 days[¥]	New users	255/18,386/57	799/42,475/77	-	0.75[&] (0.65-0.87)

NRT: Nicotine replacement therapy; IR: Incidence Rate=event/1,000 person-year; NPS: neurologic/psychiatric; PS: propensity score
Hazard Ratios calculated using Cox proportional hazards regression model
*age and sex-standardized
†Adjusted for age; sex; use of hypnotics, antipsychotics, and antidepressants; alcohol misuse; previous suicide related event; previous smoking cessation therapy; psychiatric consultation; date of initial exposure to product, number of general practice visits per year, index of multiple deprivation, UK region.
[&]Adjusted for sex; age; previous psychiatric illness or consultation; previous use of psychotropic drugs such as hypnotics, antipsychotics and antidepressants; previous self-harm; socioeconomic position; major chronic illness; number of general practice consultations in the year before the prescription; exposure to the drug before or after 2008; year of first prescription; and previous use of a smoking cessation product.
‡Restricted to those with no antidepressants in the six months before smoking cessation therapy.
[¥]Restricted to those with no previous antidepressant use

As depicted in Table 1, the 95% confidence interval of the outcome risk estimates mostly included 1.0. The only findings that achieved statistical significance are the reduced risk of outpatient neuropsychiatric visits (the VA study) and the reduced risk of initiation of antidepressant therapy (the Thomas et al. study) associated with varenicline (Table 1). However, these two outcome measures are not specific in measuring treatment emergent neuropsychiatric adverse events related to varenicline. Outpatient neuropsychiatric visits may be simply capturing pre-existing psychiatric comorbidities, rather than treatment emergent psychiatric events. Because antidepressants are also used to treat multiple other disorders, including non-psychiatric indications, prescribing of antidepressants cannot be viewed as a specific measure of incident depression.

Although none of the reviewed studies observed a significant increase in the risk of serious neuropsychiatric adverse events (i.e., neuropsychiatric hospitalization or emergency room visit, fatal or non-fatal self-harm) between varenicline and the comparator (bupropion or nicotine replacement therapy), they do not provide reassuring evidence of the absence of risk. Please see DEPI-II's review, for details of the specific limitations of these studies.

Briefly, the following study limitations have been identified:

- the completeness of ascertainment of the examined outcomes;
- the lack of validation of the diagnostic codes used to identify the examined outcomes;

- the use of bupropion (another smoking cessation drug with neuropsychiatric risk) as a comparator;
- the likely presence of "channeling bias" (sicker patients being channeled away from treatment with varenicline);
- the likely presence of residual confounding between varenicline users and nicotine replacement therapy (NRT) users; and
- the limited statistical power.

The observational studies reviewed provided evidence of insufficient quality to either rule in or rule out an increased risk of suicide, non-fatal self-harm, or neuropsychiatric hospitalizations associated with varenicline use. The available observational data also cannot be used to "cap" the varenicline-associated risk for neuropsychiatric outcomes due to the high probability of under-ascertainment of these outcomes in the existing studies. Therefore the true upper limit of the 95% confidence interval for varenicline-associated neuropsychiatric risk is unknown based on these data. It is our hope that the required post-marketing clinical trial that the sponsor is conducting may allow for more complete risk ascertainment, even though the generalizability of the findings may be limited.

Division of Biostatistics VII summary of meta-analyses[16]

A meta-analysis was conducted to evaluate the risk of psychiatric events associated with varenicline relative to placebo in two sets of trials:

- A set of 5 Phase III/IV clinical trials that captured the risk of suicidal ideation and behavior using the Columbia Suicide Severity Rating Scale (C-SSRS). This set of trials is referred to as the "5-Study Cohort". It consisted of 1907 randomized subjects: 1130 subjects randomized to varenicline and 777 subjects randomized to placebo.

- A set of 18 Phase II-IV clinical trials, including the trials in the 5-Study Cohort, which captured psychiatric adverse events through MedDRA codes. This set of trials is referred to as the "18-Study Cohort". It consisted of 8521 randomized subjects: 5072 subjects randomized to varenicline and 3449 subjects randomized to placebo.

To characterize the risk of psychiatric events several endpoints of interest were analyzed.

[16] This summary was prepared by the Division of Biostatistics VII (DB-VII) for inclusion in the briefing document for the Chantix Advisory Committee scheduled for October 16, 2014. The reader is referred to DB-VII's full review of the S-036 labeling supplement (dated 9/18/14) for more detail.

- Percent of subjects responding "yes" for suicidal ideation (any type) and/or suicidal behavior (any type) based on the C-SSRS.
- Percent of subjects who experienced an Adverse Event (AE) in the Suicide/Self-injury MedDRA Standardized MedDRA Query (SMQ).
- Percent of subjects who experienced an adverse event in the Hostility/Aggression MedDRA SMQ.
- Percent of subjects who experienced an adverse event in the MedDRA Psychiatric disorders system organ class (SOC).
- Percent of subjects experiencing an event in the composite endpoint[17] specified in ongoing trial A3051123 intended to fulfill the PMR issued in 2008 (PMR endpoint).

Table 2 summarizes the meta-analysis of psychiatric adverse events observed while patients were on randomized treatment or within a window of 30 days after treatment discontinuation. This meta-analysis showed no evidence of increased risk of psychiatric adverse events associated with varenicline relative to placebo.

Table 2. Summary of Meta-Analysis of Treatment Emergent Endpoints

Endpoint	No. Trials	Total events	RR (95% CI)
Suicidal Ideation or Behavior	5	55	0.79 (0.46, 1.36)
Suicide / Self-Injury SMQ	18	25	0.45 (0.19, 1.07)
Hostility / Aggression SMQ	18	46	1.10 (0.60, 2.03)
Psychiatric Disorders SOC	18	981	1.03 (0.84, 1.25)
PMR endpoint	18	245	0.85 (0.64, 1.13)

The meta-analysis has the following limitations:

- All analyses in the 18-Study Cohort were conducted retrospectively. Adverse events of interest were not collected prospectively and, therefore, it is possible that some adverse events may have been underreported in these trials. Specifically, as shown in Section 4.2 of the statistical background document, the suicide/self-injury SMQ did not capture some suicide-related adverse events when compared to the C-SSRS instrument. It is possible that the other SMQs in the meta-analysis may have also failed to capture some psychiatric adverse events.

[17] PMR endpoint is defined as "at least one treatment emergent "severe" adverse event of anxiety, depression, feeling abnormal, or hostility and/or the occurrence of at least one treatment emergent "moderate" or "severe" adverse event of: agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal ideation, suicidal behavior, or completed suicide."

- Forty-eight out of the 55 events in the analysis of suicidal ideation and behavior based on the C-SSRS instrument were observed in two trials that enrolled patients with history of schizophrenia or depression. Only seven events were observed in the other three trials that collected the C-SSRS.

- MedDRA SMQs and SOCs may include adverse events of different severities. It is possible that the SMQs in this meta-analysis may not be adequate to characterize the risk of rare but severe adverse events.

Discussion

Generally, when we think about the quality of evidence, we order from strongest to weakest -- randomized controlled trial data, data from observational studies, and case reports/case series. The original signal for serious neuropsychiatric events came from cases reported to the FDA and described in the medical literature. In this supplement, Pfizer argues (b) (4)

As summarized above, DB VII and DEPI-II have concerns about the validity of the findings from Pfizer's meta-analyses and the published observational studies. The limitations of the findings described in each of their reviews and summarized in this document raise questions as to how to interpret the reassuring findings of the meta-analyses and observational studies.

Furthermore, when FDA issued the postmarket requirement for the randomized controlled trial to evaluate the neuropsychiatric events with varenicline, we said that observational studies would not be adequate to address this safety question. This decision was made because there was a lack of confidence that the kinds of coded data used in observational studies could capture the neuropsychiatric events of interest. In fact, the neuropsychiatric outcome of interest for the required randomized controlled trial was crafted as a composite outcome of a series of neuropsychiatric events of a certain severity to specifically capture the kinds of events described in the spontaneous reports.

Based on FDA's review of the meta-analyses and observational studies submitted by Pfizer, FDA has determined that some information about this data should be included in the varenicline labeling so that prescribers have a full picture of what analyses and studies have been conducted to enhance the understanding of varenicline-associated serious neuropsychiatric events.

However, the determination (b) (4) is a decision for which there is little precedent. Because of the serious nature of the neuropsychiatric events described in postmarket spontaneous reports, and some limitations of the meta-analyses and observational studies that have

been discussed in this document, FDA has determined that an Advisory Committee discussion is essential to provide guidance to FDA on this matter.

Recommendations

I recommend approval of the labeling agreed upon by FDA and Pfizer at the September 8th and 16th, 2014 teleconferences and submitted to the Agency on September 18, 2014, primarily consisting of revisions to section 5.1 Neuropsychiatric Symptoms and Suicidality, but also including a minor clarification in the Boxed Warning.

Further discussion of this issue will occur at the October 16, 2014 advisory committee meeting.

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/s/

JUDITH A RACOOSIN
09/19/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021928/S-036

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES META-ANALYSIS

NDA / Serial Number:	021928 /S-036
Drug Name:	Chantix (varenicline) tablet; 0.5 mg and 1 mg
Indication(s):	Aid to smoking cessation
Applicant:	Pfizer, Inc.
Date(s):	PDUFA goal date: February 8, 2015
Review Priority:	Standard
Biometrics Division:	Division VII
Statistical Reviewer:	Eugenio Andraca-Carrera, Ph.D.
Concurring Reviewers:	Mat Soukup, Ph.D., Team Lead, DB VII Mark Levenson, Deputy Division Director, DB VII
Medical Division:	Division of Anesthesia, Analgesia, and Addiction Products
Clinical Team:	Team Lead: Celia Winchell, M.D. Deputy Director of Safety: Judy Racoosin, M.D.
Project Manager:	Ayanna Augustus

Keywords: Smoking cessation, neuropsychiatric safety, meta-analysis

1 Executive Summary

Spontaneous reports of adverse events have linked varenicline with a potential increase in neuropsychiatric adverse events. In order to evaluate this risk, the Sponsor conducted a retrospective meta-analysis of randomized clinical trials comparing varenicline relative to placebo. The Sponsor conducted analyses in two sets of trials: a set of 5 clinical trials that captured the risk of suicidal ideation and behavior using the Columbia Suicide Severity Rating Scale (C-SSRS); and a set of 18 trials that captured neuropsychiatric adverse events through MedDRA codes.

The endpoints in the Sponsor's meta-analysis were:

- Percent of subjects responding "yes" for Suicidal Ideation (any type) and/or Suicidal Behavior (any type) based on the C-SSRS.
- Percent of subjects who experienced an Adverse Event (AE) in the Suicide/Self-injury MedDRA Standardized MedDRA Query (SMQ).
- Percent of subjects who experienced an adverse event in the Hostility/Aggression MedDRA SMQ.
- Percent of subjects who experienced an adverse event in the MedDRA Psychiatric Disorders System Organ Class (SOC).

In addition to these endpoints, the Agency examined the composite endpoint pre-specified in the ongoing trial A3051123 (not included in the meta-analysis), intended to fulfill the PMR requirement issued in 2008. This endpoint includes 241 MedDRA terms for neuropsychiatric events. Analyses of all endpoints were conducted on treatment emergent events, defined as events that occurred while patients were on randomized treatment plus a window of 30 days after treatment discontinuation.

1.1 Statistical Issues and Findings

Table 1 shows a summary of the meta-analyses of treatment emergent neuropsychiatric adverse events. These analyses showed no evidence of increased risk associated with varenicline relative to placebo.

The meta-analysis conducted by the Sponsor has the following limitations:

- The suicide/self-injury MedDRA SMQ did not capture some suicide related adverse events when compared to the C-SSRS instrument. It is possible that other MedDRA terms included in the meta-analysis may have also failed to capture neuropsychiatric adverse events of interest.

- 48 out of the 55 events in the analysis of suicidal ideation and behavior based on the C-SSRS instrument were observed in two trials that enrolled patients with a history of schizophrenia or depression. The conclusions of this analysis may or may not be

generalizable to a population without these conditions. Only seven events were observed in the other three trials that collected the C-SSRS.

- MedDRA SMQs and SOCs may include adverse events of different severities. It is possible that the SMQs in this meta-analysis may not be adequate to capture and characterize the risk of rare but severe adverse events.

Table 1. Treatment Emergent Neuropsychiatric Adverse Events

Endpoint	RR (95% CI)
C-SSRS Suicidal Ideation or Behavior	0.79 (0.46, 1.36)
Suicide / Self-Injury SMQ	0.45 (0.19, 1.07)
Hostility / Aggression SMQ	1.10 (0.60, 2.03)
Psychiatric Disorders SOC	1.03 (0.84, 1.25)
PMR Endpoint	0.85 (0.64, 1.13)

2 Introduction

2.1 Product Description and Regulatory Background

Chantix (varenicline) was approved by FDA on May 10, 2006 as an aid to smoking cessation. The approved dose regimen is 1-mg twice daily (1 mg BID) for 12 weeks starting with a 1-week titration.
In February of 2009, the label for CHANTIX was modified to add a boxed warning regarding neuropsychiatric events. This change was prompted by spontaneous event reports of adverse events among patients taking CHANTIX. Additional information regarding this risk was also added to section 5.1 WARNINGS and PRECAUTIONS of the label.

On April 8th, 2014, Pfizer submitted a meta-analysis for review by the Agency to evaluate the risk of neuropsychiatric adverse events associated with varenicline relative to placebo in two sets of trials:

- A set of 5 Phase III/IV clinical trials that captured the risk of suicidal ideation and behavior using the Columbia Suicide Severity Rating Scale (C-SSRS). This set of trials is referred to as the "5-Study Cohort".

- A set of 18 Phase II-IV clinical trials, including the trials in the 5-Study Cohort, which captured psychiatric adverse events through spontaneous adverse events reports coded using the Medical Dictionary for Regulatory Activities (MedDRA).

2.2 Trial Database

The trials included in the 5-Study Cohort randomized a total of 1907 patients: 1130 to varenicline and 777 to placebo. These trials had a treatment phase of 12 weeks and off-treatment follow-up ranging from 30 days to 40 weeks. The total duration of these trials varied from 12 weeks + 30 days to 52 weeks. The inclusion criteria and objectives of the trials in the 5-Study cohort were heterogeneous. In particular, trial A3051072 was the only trial in the program that studied patients with a history of schizophrenia and trial A3051122 was the only trial that studied patients with a history of depression.

The 18-Study Cohort includes the 5 trials in the 5-Study Cohort plus 13 additional trials. These trials randomized 5072 patients to varenicline and 3449 patients to placebo. An additional 795 patients in 3 trials were randomized to Zyban. Patients randomized to Zyban were not included in any analyses and will not be discussed further in this review. All trials in the 18-Study Cohort had a treatment phase of 12 weeks, except for the dose ranging trial A3051002, which had a treatment phase of 6 weeks and trial A3051037, which was designed to evaluate long-term safety and had a treatment phase of 52 weeks.
A summary of the design characteristics of the 18 trials in the meta-analysis is shown in Table 2.

Table 2. List of Trials Included in the Meta-Analysis

Study	Population / Goal	Duration		Sample Size		
		On treatment	Total follow-up[1]	Varenicline	Placebo	Zyban
5-Study Cohort						
A3051072	Schizophrenia	12 weeks	24 weeks	84	43	-
A3051095	Flexible quit date	12 weeks	24 weeks	486	165	-
A3051115	Assessment of neuropsychiatric symptoms	12 weeks	12 weeks + 30 days	55	55	-
A3051122	Depression	12 weeks	52 weeks	256	269	-
A3051139	Re-treatment	12 weeks	52 weeks	249	245	-
PHASE 2						
A3051002	Dose-ranging	6 weeks	52 weeks	377	123	126
A3051007	Titration	12 weeks	52 weeks	506	121	-
A3051016	Flexible dosing	12 weeks	52 weeks	157	155	-
A3051037	Long-term safety	52 weeks	52 weeks	251	126	-
A3051046_48	Study in Japan	12 weeks	52 weeks	464	154	-
PHASE 3						
A3051028	Zyban comparison	12 weeks	52 weeks	349	344	329
A3051036	Zyban comparison	12 weeks	52 weeks	343	340	340
A3051045	Taiwan and Korea	12 weeks	24 weeks	126	124	-
A3051049	CV disease	12 weeks	52 weeks	353	350	-
A3051054	COPD	12 weeks	52 weeks	248	251	-
A3051055	Multinational Asian sites	12 weeks	24 weeks	165	168	-
PHASE 4						
A3051080	Africa, Mid-East, S. America	12 weeks	24 weeks	390	198	-
A3051104	Smokeless tobacco	12 weeks	26 weeks	213	218	-
			TOTAL	**5072**	**3449**	**795**

[1]Including duration on treatment

2.3 Data Sources

The Sponsor compiled the data necessary to conduct analyses of neuropsychiatric adverse events into the following datasets:

- Ae5trm.xpt contained information on neuropsychiatric adverse events in the 5-Study Cohort.
- Aetrim.xpt contained information on neuropsychiatric adverse events in the 18-Study Cohort.
- Tteve.xpt contained the data necessary to conduct time to event analyses of neuropsychiatric adverse events.
- Satrim.xpt contained data for all MedDRA-coded adverse events in the 18-Study Cohort.

The Sponsor submitted a meta-analysis report and a Statistical Analysis Plan together with these datasets. These documents were reviewed by the FDA's biostatistics review team. The latest datasets used in this review were submitted by the Sponsor on August 1st, 2014.

The following folder available within the CDER Electronic Document Room (EDR) was used to access these datasets:

\\Cdsesub1\evsprod\NDA021928

The format, content and documentation of the data submitted in support of NDA 21928 were adequate to conduct a statistical review of the meta-analysis of neuropsychiatric adverse events conducted by the Sponsor.

All tables and figures in this review were created by the FDA biostatistics review team using the datasets listed above.

3 Statistical Evaluation

The meta-analysis of randomized clinical trials discussed in this document was conducted by the Sponsor to assess the risk of neuropsychiatric adverse events associated with varenicline. This meta-analysis was conducted retrospectively to address the potential signal for adverse events reported in spontaneous reports of this product. The meta-analysis Statistical Analysis Plan (SAP) was not submitted for review by the FDA; it was submitted at the same time as the meta-analysis final report.

Note that this submission is intended to support labeling of safety with no information to support efficacy.

3.1 Evaluation of Safety

3.1.1 Endpoints

The meta-analysis SAP listed several safety endpoints of interest. Below are the sponsor identified safety endpoints of interest according to the database in which they were evaluated.

3.1.1.1 Five Study Cohort Endpoints

- Percent of patients responding "yes" for suicidal ideation (any type) and/or suicidal behavior (any type) based on the C-SSRS.
- Percent of patients responding "yes" to non-suicidal self-injurious behavior based on the C-SSRS.

The C-SSRS is a questionnaire designed to assess suicidality that has been used extensively in research and clinical practice settings. The adverse events related to suicidal ideation and/or behavior using the C-SSRS in the 5-Study Cohort were collected prospectively.

3.1.1.2 Eighteen Study Cohort Endpoints

- Percent of patients who experienced an Adverse Event (AE) in the Suicide/Self-injury MedDRA Standardized MedDRA Query (SMQ).
- Percent of patients who experienced an adverse event in the Hostility/Aggression MedDRA SMQ.
- Percent of patients who experienced an adverse event in the MedDRA Psychiatric disorders system organ class (SOC).

The MedDRA preferred terms that comprise the suicide/self-injury SMQ, the hostility/aggression SMQ and the psychiatric disorders SOC are listed in the Appendix. These composite endpoints include adverse events of all severities, ranging from mild to severe or fatal. These adverse events were not pre-specified endpoints of interest in the 18 trials and were collected through routine reports of adverse events.

3.1.1.3 PMR Endpoint

The FDA review team considered an additional endpoint that was not included in the Sponsor's submission. This endpoint is based on the primary endpoint pre-specified in trial A3051123 which is an ongoing randomized controlled trial, intended to fulfill the post-marketing requirement (PMR) issued in 2008. This trial is designed to assess the neuropsychiatric safety of varenicline relative to placebo in patients with a history of psychiatric disorders. This trial, still under way, is not included in the meta-analysis discussed in this document.

The primary pre-specified safety endpoint in trial A3051123 is a composite of "*at least one treatment emergent "severe" adverse event of anxiety, depression, feeling abnormal, or hostility and/or the occurrence of at least one treatment emergent "moderate" or "severe" adverse event of: agitation, aggression, delusions, hallucinations, homicidal*

ideation, mania, panic, paranoia, psychosis, suicidal ideation, suicidal behavior, or completed suicide." Overall, this endpoint includes 241 MedDRA terms in the 16 components listed in the definition quoted above. These terms were collected as part of routine reports of adverse events in the 18-Study Cohort and were not blindly adjudicated. This endpoint will be referred to as the "Post-marketing requirement (PMR) endpoint". Note that this endpoint only includes adverse events above a pre-defined threshold of severity for each type of event.

3.1.2 Statistical Methodologies

This section describes the methodology used by the Sponsor to conduct their meta-analyses. The FDA review team reproduced the Sponsor's analyses using the same methodology unless noted otherwise.

Suicidal ideation and behavior captured in the C-SSRS were analyzed through a Poisson regression model with study, treatment group and pre-dose history of suicidal ideation as covariates and the natural logarithm of the time at risk as an offset. The parameter of interest was the risk ratio (RR) of the C-SSRS endpoints comparing patients randomized to varenicline to patients randomized to placebo.

Neuropsychiatric adverse events coded as MedDRA terms were analyzed by the Sponsor through the Mantel-Haenszel risk ratio and its corresponding 95% confidence interval comparing varenicline to placebo. This approach was used to analyze the Suicide/Self Injury SMQ, Hostility/Aggression SMQ and Psychiatric disorders SOC. The implementation of the Mantel-Haenszel risk ratio by the FDA review team was different from the Sponsor's implementation. We used model weights based on the total number of events and the total number of patient-years of exposure on treatment plus 30 days within each trial, whereas the Sponsor used weights using only the number of events observed in the placebo arm and the patient years of exposure on varenicline divided by the total years of exposure in each trial. Both approaches produced similar estimates of the risk ratio.

The FDA review team analyzed the PMR endpoint through the Mantel-Haenszel risk ratio and its corresponding 95% confidence interval comparing varenicline to placebo based on treatment emergent outcomes and exposure.

The Mantel-Haenszel risk ratio only uses information from trials with at least one reported event. In order to assess the impact of trials with zero events on estimates of risk, we estimated the Mantel-Haenszel risk difference associated with varenicline relative to placebo for each of the endpoints of interest based on treatment emergent outcomes and exposure. The risk difference uses information from all trials, including those with no reported events.

All confidence intervals were calculated at a nominal 95% confidence level. No corrections were made for multiple comparisons.

For each safety endpoint, the primary set of analyses were conducted on treatment emergent events, defined as events that occurred while patients were on randomized treatment plus a window of 30 days after treatment discontinuation (i.e. this is referred to as an on-treatment analysis). Secondary analyses were conducted on events observed during the full follow-up time in each trial (i.e. this is referred to as an on-study analysis).

3.1.4 Patient Disposition, Demographics and Baseline Characteristics

3.1.4.1 Demographics and Baseline Characteristics

Table 3 shows pooled baseline demographic characteristics as well as history of smoking, alcohol use and suicidal ideation for subjects randomized to varenicline or placebo in the 18 trials in the meta-analysis. Overall, the majority of subjects were male, had a mean age of approximately 45 years at baseline, and a majority of subjects were categorized as White. All the characteristics summarized in this table appear balanced between the two treatment arms.

Table 3. Pooled Baseline Characteristics of Patients in the 18 Trials

	Varenicline (*N = 5072*)	**Placebo** (*N = 3449*)
Percent female	35.8%	39.6%
Age ± SD (years)	44.7 ± 12.2	45.5 ± 12.3
≤ 30 years	14.4%	13.0%
31 – 45 years	37.0%	36.7%
46 - 60 years	38.5%	38.6%
> 60 years	10.1%	11.7%
Race		
White	66.8%	69.8%
Black	6.4%	6.6%
Asian	18.8%	16.0%
Other	8.0%	7.6%
History of suicidal ideation	15.3%	15.4%
Mean cigarettes per day in last month ± SD	22.4 ± 9.7	22.3 ± 9.5
Patient drinks alcohol		
Yes	22.0%	20.8%
No	14.6%	13.6%
Missing	63.4%	65.6%
Has tried quitting smoking		
Using counseling	7.6%	7.6%
Using cold turkey	19.7%	19.2%
Using gum	13.5%	12.1%
Using lozenge	1.8%	2.2%

3.1.4.2 Follow-Up and Trial Disposition

Table 4 and Table 5 show the mean observed follow-up time on treatment and on study for patients enrolled in the trials included in the meta-analysis. The mean follow-up times were similar for patients randomized to varenicline or placebo.

Table 4. Mean Follow-up (days) On Treatment + 30 Days

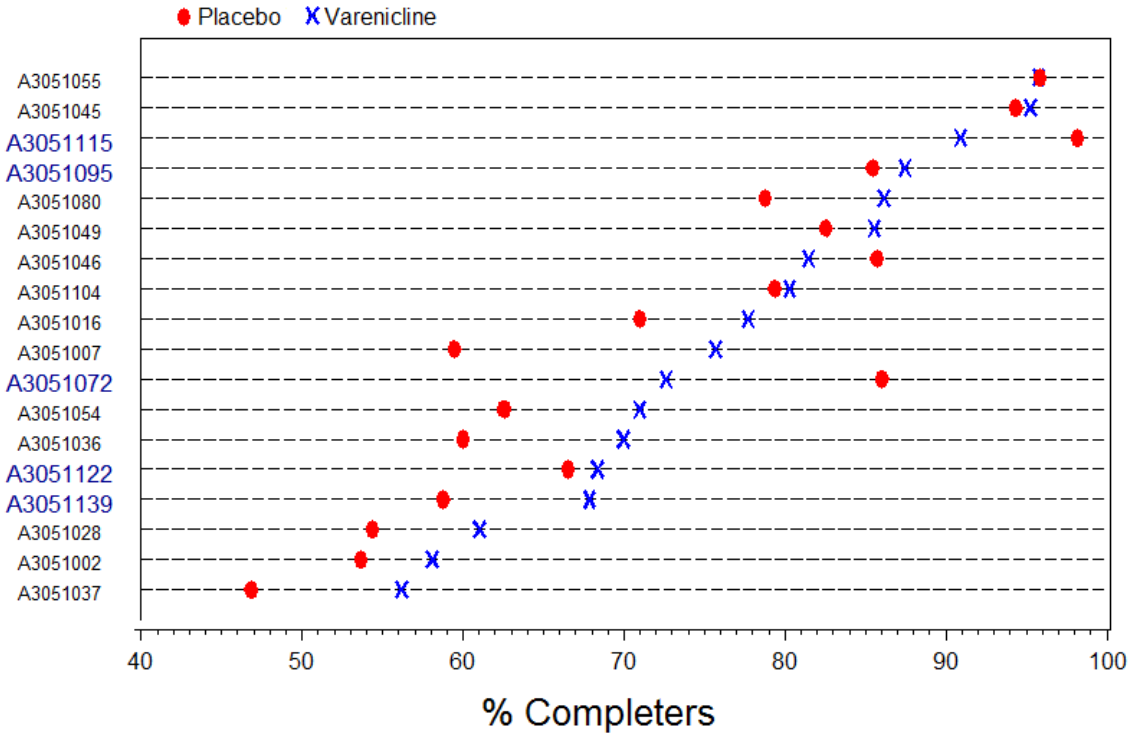
	Varenicline	Placebo
18 -Study Cohort	110	106
5 - Study Cohort	105	102

Table 5. Mean Follow-up (days) On Study

	Varenicline	Placebo
18 -Study Cohort	254	240
5 - Study Cohort	224	236

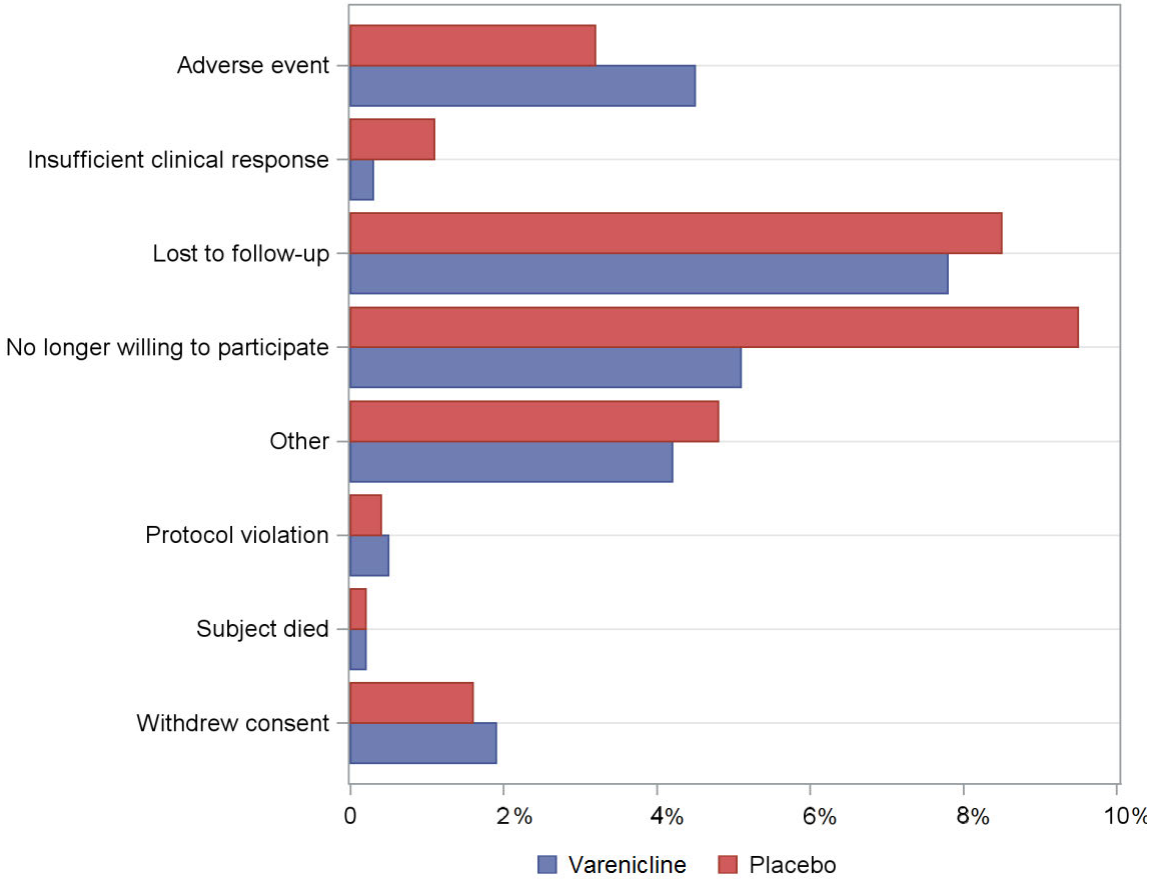
Figure 1 shows that patients randomized to varenicline were on average more likely to complete trial participation than patients randomized to placebo. The two exceptions in which patients on varenicline discontinued study enrollment at a higher rate than patients on placebo were trial 1072 (population with history of schizophrenia) and trial 1115 (assessment of neuropsychiatric symptoms). The pooled study discontinuation rate in the 18 trials was 29% on placebo and 24% on varenicline. A similar pattern was observed regarding treatment discontinuation (not shown in figures): patients randomized to varenicline were on average more likely to remain on randomized treatment than patients randomized to placebo.

Figure 1. Study Completers by Study



A pooled summary of the reasons given for trial discontinuation in the 18 trials in the meta-analysis is shown in Figure 2. Patients randomized to varenicline were more likely to discontinue study participation due to adverse events than patients randomized to placebo. Patients randomized to placebo were more likely to discontinue study participation due to being “no longer willing to participate” or being lost to follow-up. The observed rate of adverse events in the psychiatric disorders SOC events was similar between study completers and non-completers during their recorded follow-up time (not shown in tables).

Figure 2. Reason for Trial Discontinuation



3.1.3 Analysis Results

This section presents the analyses of the treatment emergent endpoints listed in Section 3.1.1.

3.1.4.1 Suicidal ideation and/or suicidal behavior based on the C-SSRS

Figure 3 shows that 28 out of 1130 (2.5%) patients randomized to varenicline (with 325 patient-years of exposure) and 27 out of 777 (3.5%) patients randomized to placebo (with 217 patient-years of exposure) reported treatment emergent suicidal ideation or behavior based on the C-SSRS instrument in the 5-Study Cohort. The corresponding estimated risk ratio and 95% confidence interval for this endpoint was 0.79 (0.46, 1.36). Table 6 shows that most of these events were recorded as suicidal ideation and only two patients recorded suicidal behavior. One patient randomized to varenicline experienced both suicidal ideation and suicidal behavior.

Forty eight (48) out of the 55 patients with suicidal ideation or behavior were enrolled in two trials: A3051072, which enrolled patients with a history of schizophrenia, and A3051139, which enrolled patients with a history of depression. Only seven events were observed in the other three trials that used the C-SSRS instrument.

Figure 3. Suicidal Ideation or Behavior based on C-SSRS

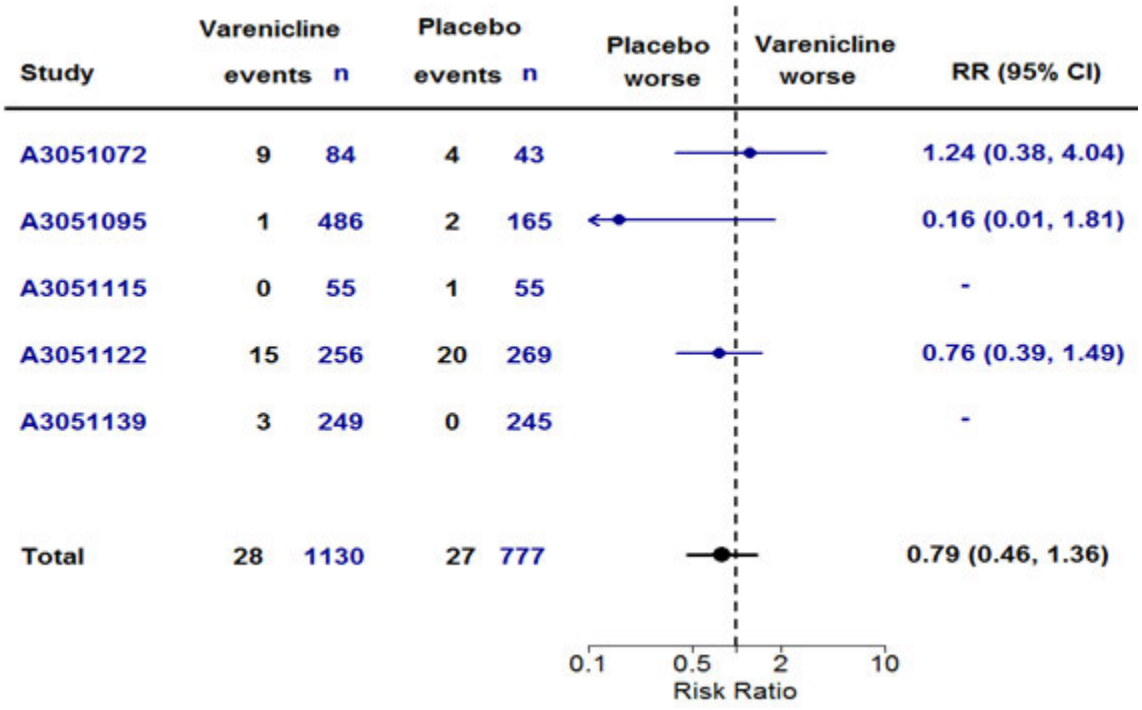


Table 6. Suicidal Ideation and Suicidal Behavior based on C-SSRS

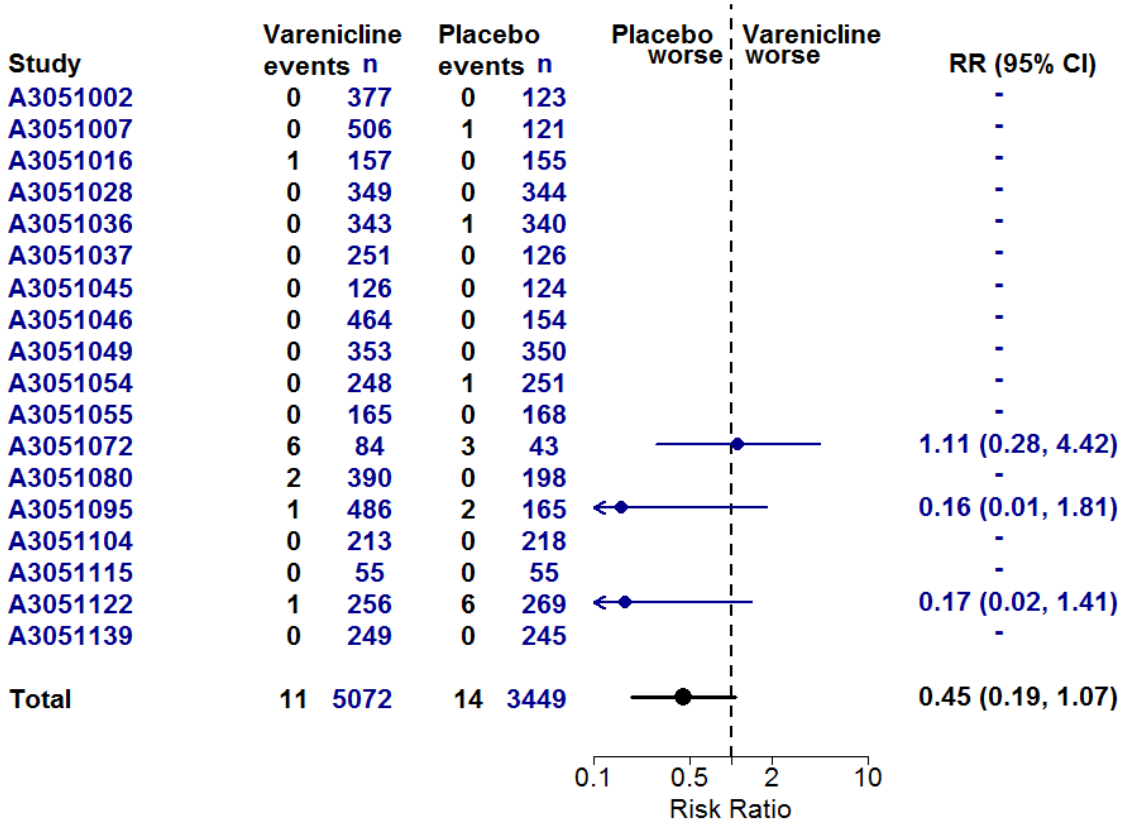
	Varenicline n = 1130	**Placebo** n = 777	**Risk Ratio** 95% CI
Suicidal Ideation	28 (2.48%)	26 (3.35%)	0.82 (0.48, 1.42)
Suicidal Behavior	1 (0.09%)	1 (0.13%)	*

*Not calculated due to the low number of events

3.1.4.2 Suicide/Self-Injury SMQ

Of the 8521 randomized patients 35 reported a treatment emergent adverse event in the suicide and self-injury SMQ in the 18-Study Cohort: 11 out of 5072 (0.22%) patients randomized to varenicline and 14 out of 3449 (0.41%) patients randomized to placebo. Figure 4 shows the corresponding estimated risk ratio (RR) and 95% confidence intervals for these data. The estimated meta-analysis RR for this SMQ was 0.45 (0.19, 1.07). Nine of the 25 events were observed in trial A3051072, which studied a population of patients with history of schizophrenia.

Figure 4. Treatment Emergent Events in the Suicide/Self Injury SMQ



In order to evaluate the sensitivity of the suicide and self-injury SMQ, we compared the counts of events of suicidal ideation or behavior captured in the C-SSRS instrument to the adverse events in the suicide and self-injury SMQ in the 5-Study Cohort. These were the only five trials in the meta-analysis that captured suicidal ideation or behavior through both the C-SSRS and MedDRA terms. The results of this comparison are shown in Table 7. There were 37 patients in the 5-Study Cohort with recorded suicidal ideation or behavior in the C-SSRS who did not have an event recorded in the suicide/self-injury SMQ, and one patient with an event in the SMQ who did not have suicidal ideation according to the C-SSRS. Trial A3051122, which enrolled patients with a history of depression, had 28 patients with an event recorded in the C-SSRS but not on the MedDRA suicide and self-injury SMQ.

Table 7. Comparison of C-SSRS to MedDRA SMQ on Suicidality

Trial	Suicidality on C-SSRS	Suicidal / Self-Injury SMQ
A3051072	13	9
A3051095	3	3
A3051115	1	0
A3051122	35	7
A3051139	3	0

Reviewer's Comment: *These inconsistencies may reflect underreporting of adverse events of suicide or self-injury captured through MedDRA coded adverse events that are collected in an unsolicited manner (i.e., patients must voluntarily report them to the study investigator). As such, we recommend that assessment of suicidality by based upon the 5 Study Cohort using the C-SSRS instrument.*

3.1.4.3 Hostility/Aggression SMQ

A total of 46 patients reported treatment emergent hostility and aggression SMQ events: 28 out of 5072 (0.55%) on varenicline and 18 out of 3449 (0.52%) on placebo. The estimated RR and 95% confidence interval for this SMQ associated with varenicline was 1.10 (0.60, 2.03).

Figure 5. Treatment Emergent Events in the Hostility/Aggression SMQ

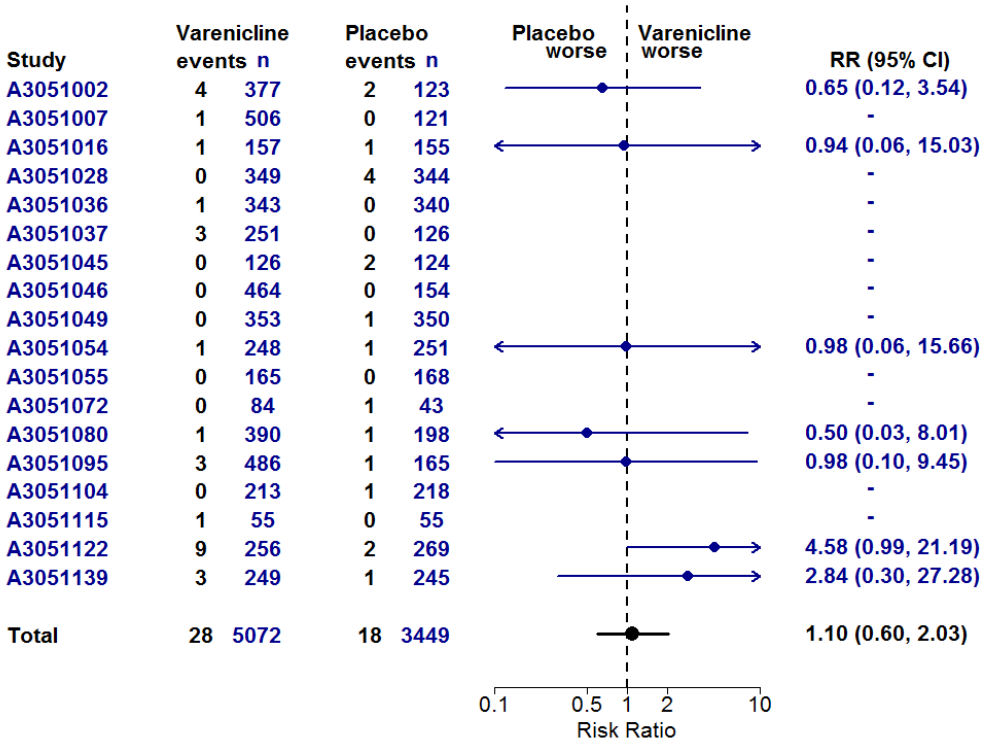


Table 8 shows that all but one of the adverse events in the hostility and aggression SMQ were reported as aggression, anger or hostility. One event was reported as sexual abuse in one patient randomized to varenicline.

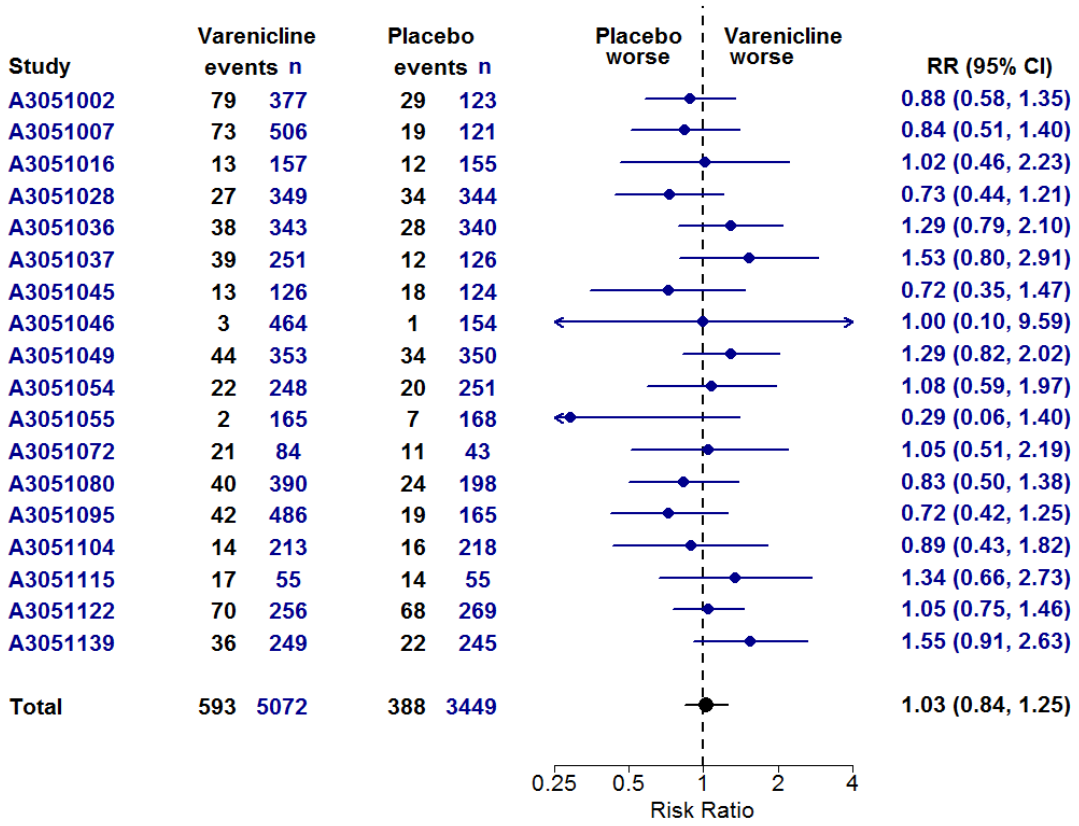
Table 8. Patients with an Adverse Event in the Hostility/Aggression SMQ

	Varenicline n = 5072	**Placebo** n = 3449
Total	**28 (0.55%)**	**18 (0.52%)**
Aggression	10 (0.20%)	7 (0.20%)
Anger	12 (0.24%)	12 (0.35%)
Hostility	8 (0.16%)	2 (0.06%)
Sexual Abuse	1 (0.02%)	0

3.1.4.4 Psychiatric Disorders SOC Excluding Sleeping Disorders

The psychiatric disorders SOC includes events such as anxiety, cognitive disorders, deliria, dementia, depression, mood and personality disorders, sexual dysfunctions, and suicidal behaviors. A total of 981 patients from the 18-Study Cohort had treatment emergent adverse events in this SOC: 593 out of 5072 on varenicline (11.69%) and 388 out of 3449 on placebo (11.25%). The estimated RR and 95% confidence interval for the composite of any event in this SOC, excluding sleeping disorders, associated with varenicline was 1.03 (0.84, 1.25).

Figure 6. Treatment Emergent Events in the Psychiatric Disorders SOC



In Table 9 below, the most common events in the psychiatric disorders SOC were "Anxiety disorders and symptoms" observed in 459 total patients, "Depressed mood disorders and disturbances", observed in 287 total patients, and "mood disorders and disturbances not elsewhere classified" observed in a total of 169 total patients. The results show a similar incidence of common psychiatric events in patients treated with varenicline compared to patients treated with placebo.

Table 9. Psychiatric Adverse Events Occurring in ≥ 1% of Patients from Pooled Analysis of 18 Clinical Trials

	Varenicline (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

3.1.4.5 PMR Endpoint

The PMR endpoint is a composite that includes 241 MedDRA terms in 16 categories as described in Section 3.1.1. In the 18 trials in the meta-analysis, 146 patients on varenicline (2.9%) and 99 patients in placebo (2.9%) reported at least one treatment emergent event in this composite endpoint. The estimated RR and 95% confidence interval for this endpoint associated with varenicline was 0.85 (0.64, 1.13).

Table 10 shows the categories that comprise the PMR endpoint. The largest number of reported events was reported in the agitation category (132 total events), the mania category (39 events), and the anxiety category (30 events).

Table 10. Treatment Emergent PMR Endpoint

	Varenicline n = 5072	Placebo n = 3449
Composite event	**146 (2.9%)**	**99 (2.9%)**
Moderate or severe		
Aggression	13 (0.3%)	12 (0.3%)
Agitation	80 (1.6%)	52 (1.5%)
Delusions	0	2 (0.1%)
Hallucination	5 (0.1%)	3 (0.1%)
Mania	28 (0.6%)	11 (0.3%)
Panic	11 (0.2%)	4 (0.1%)
Paranoia	1 (0.0%)	1 (0.0%)
Psychosis	7 (0.1%)	6 (0.2%)
Suicidal ideation / behavior	8 (0.2%)	10 (0.3%)
Severe		
Anxiety	11 (0.2%)	19 (0.6%)
Depression	15 (0.3%)	6 (0.2%)
Feeling abnormal	0	1 (0.0%)

3.1.4.6 Sensitivity Analyses Based on Full On-Study Follow-Up Time

The analyses discussed in sections 3.1.4.1 through 3.1.4.5 were conducted on treatment emergent events, defined as events that occurred while patients were on randomized treatment plus a window of 30 days after treatment discontinuation. Table 11 shows the estimated risk ratio for these adverse events based on the full follow-up time from randomization to study completion or discontinuation. These analyses were consistent with the analyses based on treatment emergent adverse events and show no evidence of increased risk of neuropsychiatric adverse events associated with varenicline.

Table 11. Meta-Analysis Results Based on Full Study Follow-Up Time

Endpoint	No. Trials	No. of Events (%)		RR (95% CI)
		Varenicline	Placebo	
C-SSRS Suicidal Ideation or Behavior	5	46 (4.07%)	32 (4.12%)	1.11 (0.71, 1.76)
Suicide / Self-Injury SMQ	18	16 (0.32%)	14 (0.41%)	0.67 (0.31, 1.45)
Hostility / Aggression SMQ	18	28 (0.55%)	18 (0.52%)	1.05 (0.57, 1.92)
Psychiatric Disorders SOC	18	618 (12.18%)	400 (11.60%)	0.96 (0.83, 1.11)
PMR endpoint	18	153 (3.02%)	99 (2.87%)	0.90 (0.68, 1.20)

3.1.4.7 Sensitivity Analyses – Risk Difference

The Mantel-Haenszel risk ratio estimated in Sections 3.1.4.1 through 3.1.4.6 only uses information from trials with at least one reported event. Trials with no events do not contribute to the estimated risk ratios. In order to assess the impact of trials with zero events on the meta-analysis, we estimated the Mantel-Haenszel risk difference associated with varenicline relative to placebo for each of the endpoints of interest. The risk difference uses information from all trials, including those with no reported events. The results of these analyses are summarized in Table 12. The estimated risk differences show no evidence of increased risk of neuropsychiatric adverse events associated with varenicline relative to placebo.

Table 12. Risk Difference of Treatment Emergent Neuropsychiatric Adverse Events

Endpoint	Varenicline N = 5072	Placebo N = 3449	RD per 100 PY (95% CI)
C-SSRS Suicidal Ideation or Behavior	28 (2.5%)	27 (3.5%)	-1.63 (-6.81, 3.55)
Suicide / Self-Injury SMQ	11 (0.22%)	14 (0.41%)	-0.74 (-1.57, 0.09)
Hostility / Aggression SMQ	28 (0.55%)	18 (0.52%)	0.17 (-0.92, 1.27)
Psychiatric Disorders SOC	593 (11.69%)	388 (11.25%)	0.44 (-4.68, 5.57)
PMR endpoint	146 (2.9%)	99 (2.9%)	-1.31 (-3.84, 1.21)

4 Summary and Conclusions

4.1 Statistical Issues

A potential risk for neuropsychiatric adverse events associated with varenicline has been observed in spontaneous adverse event reports. The Sponsor conducted a meta-analysis of randomized clinical trials to evaluate this risk associated with varenicline relative to placebo. The meta-analysis was conducted in two sets of trials:

- A set of 5 Phase III/IV clinical trials that captured the risk of suicidal ideation and behavior using the Columbia Suicide Severity Rating Scale (C-SSRS). These five trials randomized 1897 total patients: 1130 to varenicline and 777 to placebo.

- A set of 18 Phase II-IV clinical trials, including the trials in the 5-Study Cohort, which captured psychiatric adverse events through MedDRA codes. These eighteen trials randomized 8521 patients: 5072 to varenicline and 3449 to placebo.

The Sponsor conducted their meta-analysis retrospectively and their Statistical Analysis Plan was not submitted in advance for review by the Agency. The endpoints analyzed by the Sponsor were:

- Percent of subjects responding "yes" for suicidal ideation (any type) and/or suicidal behavior (any type) based on the C-SSRS.
- Percent of subjects who experienced an Adverse Event (AE) in the Suicide/Self-injury MedDRA Standardized MedDRA Query (SMQ).
- Percent of subjects who experienced an adverse event in the Hostility/Aggression MedDRA SMQ.
- Percent of subjects who experienced an adverse event in the MedDRA Psychiatric disorders system organ class (SOC).

The collection of the C-SSRS endpoints in the 5-Study cohort was actively captured using the C-SSRS instrument. The endpoints based on MedDRA terms were collected as part of standard adverse event reports in the eighteen clinical trials in the meta-analysis. In addition to these endpoints, the Agency examined the composite endpoint pre-specified in the ongoing trial A3051123, intended to fulfill the PMR requirement issued in 2008.

The analysis population of interest for all endpoints consisted of the time during which patients were on randomized treatment plus a window of 30 days after treatment discontinuation.

4.2 Collective Evidence

Table 13 shows a summary of the estimated risk ratios and corresponding 95% confidence intervals for treatment emergent neuropsychiatric adverse events associated with varenicline. These analyses showed no evidence of increased risk of neuropsychiatric adverse events associated with varenicline relative to placebo.

Table 13. Summary of Meta-Analysis of Treatment Emergent Adverse Events

Endpoint	No. Trials	Total events	RR (95% CI)
C-SSRS Suicidal Ideation or Behavior	5	55	0.79 (0.46, 1.36)
Suicide / Self-Injury SMQ	18	25	0.45 (0.19, 1.07)
Hostility / Aggression SMQ	18	46	1.10 (0.60, 2.03)
Psychiatric Disorders SOC	18	981	1.03 (0.84, 1.25)
PMR Endpoint	18	245	0.85 (0.64, 1.13)

The following limitations of the meta-analysis have been discussed in this review:

- All analyses in the 18-Study Cohort were conducted retrospectively. Adverse events of interest were not collected prospectively and therefore it is possible that some adverse events may have been underreported in these trials. Specifically, as shown in Section 3.1.4.2, the suicide/self-injury SMQ did not capture some suicide related adverse events when compared to the C-SSRS instrument. It is possible that other MedDRA terms included in the meta-analysis may have also failed to capture psychiatric adverse events of interest.

- 48 out of the 55 events in the analysis of suicidal ideation and behavior based on the C-SSRS instrument were observed in two trials that enrolled patients with a history of schizophrenia or depression. The conclusions of this analysis may or may not be generalizable to a population without these conditions. Only seven events were observed in the other three trials that collected the C-SSRS.

- MedDRA SMQs and SOCs may include adverse events of different severities. It is possible that the SMQs in this meta-analysis may not be adequate to capture and characterize the risk of rare but severe adverse events.

Appendix 1. MedDRA SMQs and Psychiatric Disorders SOC

The **Suicide/Self-injury SMQ** includes the following MedDRA Preferred Terms:

- Completed suicide
- Depression suicidal
- Intentional overdose
- Intentional self-injury
- Poisoning deliberate
- Self-injurious behavior
- Self-injurious ideation
- Suicidal behavior
- Suicidal ideation
- Suicide attempt

The **Hostility/Aggression SMQ** includes the following PTs:

- Aggression
- Amygdalotomy
- Anger
- Antisocial behavior
- Antisocial personality disorder
- Belligerence
- Borderline personality disorder
- Child abuse
- Conduct disorder
- Homicidal ideation
- Homicide
- Hostility
- Incest
- Intermittent explosive disorder
- Physical abuse
- Physical assault
- Psychopathic personality
- Sexual abuse
- Violence-related symptoms

The **Psychiatric Disorders System Organ Class**, excluding sleeping disorders, includes the following High Level Group Terms (HLGTs):

- Adjustment disorders (including subtypes)
- Anxiety disorders and symptoms
- Changes in physical activity
- Cognitive and attention disorders and disturbances
- Communication disorders and disturbances
- Deliria (including confusion)
- Dementia and amnestic conditions
- Depressed mood disorders and disturbances
- Developmental disorders NEC

- Dissociative disorders
- Disturbances in thinking and perception
- Eating disorders and disturbances
- Impulse control disorders NEC
- Manic and bipolar mood disorders and disturbances
- Mood disorders and disturbances NEC
- Personality disorders and disturbances in behaviour
- Psychiatric and behavioural symptoms NEC
- Psychiatric disorders NEC
- Schizophrenia and other psychotic disorders
- Sexual dysfunctions, disturbances and gender identity disorders
- Somatoform and factitious disorders
- Suicidal and self-injurious behaviours NEC

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/s/

EUGENIO ANDRACA-CARRERA
09/18/2014

MATTHEW J SOUKUP
09/18/2014
Concur

MARK S LEVENSON
09/18/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021928/S-036

OTHER REVIEW(S)

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

Drug Utilization Review

Date:	September 03, 2014
Reviewer:	Rajdeep Gill Pharm.D., Drug Utilization Data Analysis Acting Team Leader Division of Epidemiology II (DEPI II)
Acting Deputy Director:	Hina Mehta, Pharm.D., Acting Deputy Director for Drug Utilization Division of Epidemiology II (DEPI II)
Division Director:	Judy Staffa, Ph.D., RPh. Division of Epidemiology II (DEPI II)
Drug Name(s):	Chantix® (varenicline) tablets
Application Type/Number:	21928
Applicant/Sponsor:	Pfizer
OSE RCM #:	2014-749

This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.

CONTENTS

EXECUTIVE SUMMARY

To assist the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) prepare for an upcoming advisory committee meeting to discuss Chantix® (varenicline) and risk for neuropsychiatric events, this review analyzes the drug utilization patterns for Chantix® (varenicline) and comparator agents.

The overall sales of various smoking cessation products; prescription (Rx) and over-the-counter (OTC) products, decreased by approximately 36% from approximately 9.5 million bottles/packages sold in 2009 to 6.1 million bottles/packages sold in 2013. During 2013, prescription products accounted for approximately 52% (3.1 million bottles/packages) and OTC products accounted for approximately 48% (2.9 million bottles/packages) of the total sales of smoking cessation products.

Among prescription smoking cessation products, a vast majority of utilization was [redacted] The number of prescriptions dispensed [redacted]

The overall number of packages of OTC nicotine replacement products sold through retail settings fluctuated during the time examined with approximately 1.7 million packages sold in the 4th quarter of 2013. Among the OTC nicotine replacement products, the gum formulation accounted for the highest proportion of the total retail sales followed by lozenges and patches.

1 INTRODUCTION

1.1 BACKGROUND

The Division of Analgesia, Anesthesia and Addiction Products (DAAAP) is currently preparing for a joint meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee Meeting to be held on October 16, 2014 to discuss the risk of serious neuropsychiatric adverse events with Chantix® (varenicline) tablets (NDA 21928) and to further discuss options for addressing this risk.[1]

In preparation for the advisory committee meeting, the Division of Epidemiology II was requested to provide the drug utilization patterns for Chantix® (varenicline) as well as Zyban® (brand and generic), Nicotrol® inhaler, Nicotrol® nasal spray and over-the-counter (OTC) nicotine replacement products (patches, gum and lozenges).

[1] http://www.fda.gov/advisorycommittees/calendar/ucm394876 htm; accessed August 2014

1.2 PRODUCT LABELING

Chantix® (varenicline) is a nicotinic receptor partial agonist indicated for use as an aid to smoking cessation treatment and was approved in May 2006.[2]

Chantix® (varenicline) is available as 0.5 mg and 1mg oral tablets.

2 METHODS AND MATERIALS

2.1 DETERMINING SETTINGS OF CARE

The IMS Health, IMS National Sales Perspective™ was used to determine the various retail and non-retail channels of distribution for Chantix® (varenicline). Sales data for 2013 indicated that approximately (b) (4) [redacted]. Retail pharmacies include chain stores, independent pharmacies, and food store pharmacies. Non-retail pharmacy and mail-order/specialty pharmacy settings data were not included in this analysis.

2.2 DATA SOURCES USED

Proprietary drug utilization databases were used to conduct this analysis (see Appendix 2 for full database description).

The IMS Health, National Sales Perspectives™ database was used to provide the nationally estimated number of bottles/packages of prescription (Rx) smoking cessation products and over-the-counter (OTC) nicotine replacement products sold from manufacturers to retail and non-retail channels of distribution in the U.S. from 2009 through 2013, yearly. These sales data represent the amount of product being sold from manufacturers into the "back door" of various drug distribution outlets such as retail pharmacies, hospitals, clinics, etc.; it does not reflect what is being sold to or administered to patients directly.

The IMS Health, National Prescription Audit (NPA) was used to obtain the nationally estimated number of prescriptions dispensed for Chantix® (varenicline) as well as Zyban® (brand and generic), Nicotrol® inhaler, and Nicotrol® nasal spray through U.S. outpatient retail pharmacies from approval May 2006 through March 2014, quarterly.

The IMS Health, Total Patient Tracker (TPT) was used to obtain the nationally estimated number of patients who received a dispensed prescription Chantix® (varenicline) as well as Zyban® (brand and generic), Nicotrol® inhaler, and Nicotrol® nasal spray from U.S. outpatient retail pharmacies for years 2006 through 2013. The IMS Health, Total Patient Tracker (TPT) was also used to obtain nationally estimated number of patients who received a dispensed prescription Chantix® (varenicline) stratified by patient age (0-17, 18-24, 25-44, 45-64, 65 years and older) and sex for years 2006 through 2013.

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[2] http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021928s030lbl.pdf; label accessed August 2014

[3] IMS Health, National Sales Perspectives (NSP), Data extracted August 2014. File: NSPC 2017-749 chantix channels 08-04-14.xlsx

The OTC International Market Tracking (OTCIMS) database was used to provide the nationally estimated number of packages of OTC nicotine replacement products sold, stratified by formulation, from various U.S. outpatient retail store outlets to the consumers from 2009 through 2013, quarterly. Although these sales data show the amount of product being sold through the front end, direct patient use of the over-the-counter products is not captured as information of the actual or intended user is not captured.

3 RESULTS

3.1 SALES DATA

Figure 1 in Appendix 1 provides the nationally estimated number of bottles/packages of Rx smoking cessation products and OTC nicotine replacement products sold from manufacturers to retail and non-retail channels of distribution in the U.S. for 2009 through 2013. The overall sales of various smoking cessation products, both Rx and OTC, decreased by approximately 36% from 9.5 million bottles/packages sold in 2009 to 6.1 million bottles/packages sold in 2013. In 2009, Rx products accounted for approximately 47% (4.4 million bottles/packages) and OTC products accounted for approximately 53% (5.1 million bottles/packages) of the total sales of smoking cessations products. In 2013, Rx products accounted for approximately 52% (3.1 million bottles/packages) and OTC products accounted for approximately 48% (2.9 million bottles/packages) of the total sales of smoking cessations products.

3.2 PRESCRIPTION DATA

Figure 2 in Appendix 1 provides the nationally estimated number of dispensed prescriptions for Chantix® (varenicline) as well as Zyban® (brand and generic), Nicotrol® inhaler, and Nicotrol® nasal spray from U.S. outpatient retail pharmacies from the 2nd quarter of 2006 through the 1st quarter of 2014. The number of (b) (4) .

3.3 PATIENT DATA

Figure 3 in Appendix 1 provides the nationally estimated number of unique patients who received a dispensed prescription for Chantix® (varenicline) as well as Zyban® (brand and generic), Nicotrol® inhaler, and Nicotrol® nasal spray from U.S. outpatient retail pharmacies from 2006 through 2013. (b) (4)

(b) (4)

3.4 CHANTIX: PATIENT DATA BY AGE AND SEX

Table 1 in Appendix 1 provides the nationally estimated number of unique patients (stratified by sex and age) who received a dispensed prescription Chantix® (varenicline) from U.S. outpatient retail pharmacies from 2006 through 2013. (b) (4)

(b) (4)

3.5 OTC DATA

Figure 4 in Appendix 1 provides the number of packages of OTC nicotine replacement products, stratified by product formulation, sold from U.S. outpatient retail store outlets (point of sale) to consumers from the 1st quarter of 2009 to the 4th quarter of 2013. The overall number of packages of OTC nicotine replacement products sold fluctuated during the time examined with approximately 1.7 million packages sold in the 4th quarter of 2013. Throughout the examined time period, the gum formulation accounted for the highest proportion of the total retail sales. The number of packages of the gum formulation increased from approximately 811,000 packages (46% of the total retail sales) sold in the 1st quarter of 2009 to approximately 1.1 million packages (57% of the total retail sales) sold in the 4th quarter of 2013. During the same time period, the number of packages of the lozenge formulation decreased slightly from approximately 380,000 packages (26% of total retail sales) sold in the 1st quarter of 2009 to approximately 327,000 packages (25% of the total retail sales) sold in the 4th quarter of 2013. Meanwhile, the number of packages of the patch formulation decreased from approximately 402,000 packages (28% of total retail sales) sold in the 1st quarter of 2009 to approximately 251,000 packages (19% of the total retail sales) sold in the 4th quarter of 2013.

4 DISCUSSION

The overall findings from this review illustrate that the sales of smoking cessation products (Rx and OTC) decreased over the time period examined. The (b) (4). *Of note, we only included products that are labelled for smoking cessation in our analysis. We did not include products that may be used off-label, such as Wellbutrin (Buproprion) SR and XL and the generic equivalents.*

The OTC sales data illustrated that the number of packages of over-the-counter nicotine replacement products fluctuated over the time period examined, with the gum formulation accounting for the largest proportion of the total OTC sales.

Findings from this review should be interpreted in the context of the known limitations of the databases used. The IMS Health, IMS National Sales Perspectives™, sales data for 2013 indicated that (b) (4) These data do not provide a direct estimate of use, they represent the amount of product being sold from manufacturers into the "back door" of various drug distribution outlets (e.g. retail pharmacies, hospitals, clinics, etc.) – it does not reflect what is being sold to or administered to patients directly.

For the prescription smoking cessation products, we focused our analysis on only the outpatient retail pharmacy settings, therefore these estimates may not apply to other settings of care, such as mail-order/specialty pharmacies, clinics, and hospitals, in which these products are used.

The OTCIMS database tracks retail sales data and captures (b) (4) sales activity of over-the-counter products from retail drug stores, food stores, and mass merchandisers (excluding Wal-Mart) – retail sales data are projected to represent U.S. retailer universe. We focused our OTC analyses on only the outpatient retail settings, therefore these estimates may not apply to other settings of care such as on-line purchasing. Due to these limitations, not all of the retail sales or the household purchasing data of OTC nicotine replacement products in the U.S. is captured in this analysis, and the true extent of use of OTC nicotine replacement products is at best underestimated. Moreover, direct patient use is not available as information of the actual or intended user is not captured. As a result, a reliable estimate of direct patient use of OTC products is not possible.

All the estimates provided in this analysis (sales data, prescription data, patient data, and OTC data) are national estimates, but no statistical tests were performed to determine statistically significant changes over time or between products. Therefore, all changes over time or between products should be considered approximate, and may be due to random error.

5 CONCLUSION

The overall sales of prescription and over-the-counter smoking cessation products decreased over the time period examined. During 2013, prescription products accounted for approximately 52% (3.1 million bottles/packages) and OTC products accounted for approximately 48% (2.9 million bottles/packages) of the total sales of smoking cessation products. Among prescription products, (b) (4)

APPENDIX 1: Tables and Figures.

Figure 1.

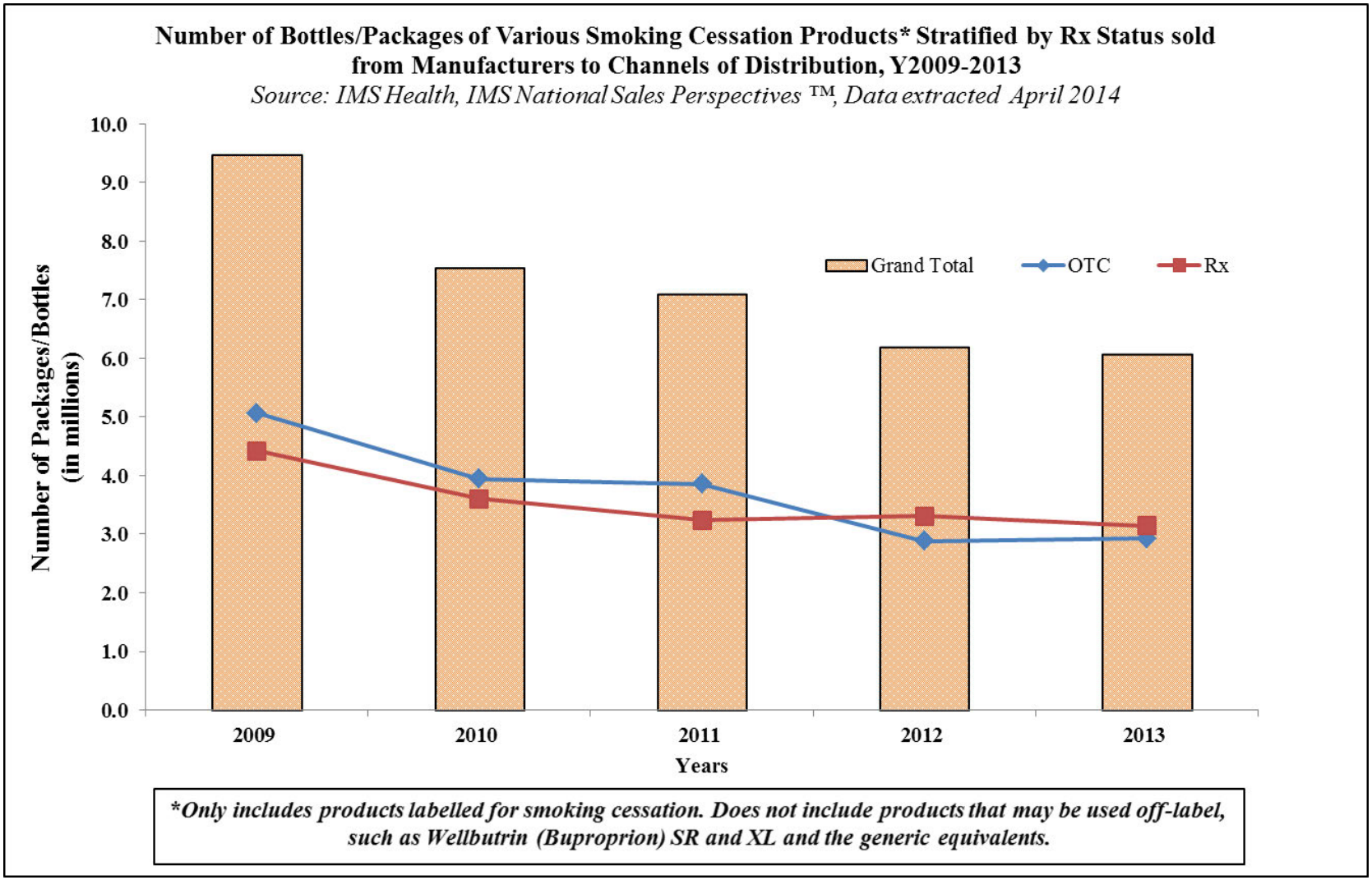

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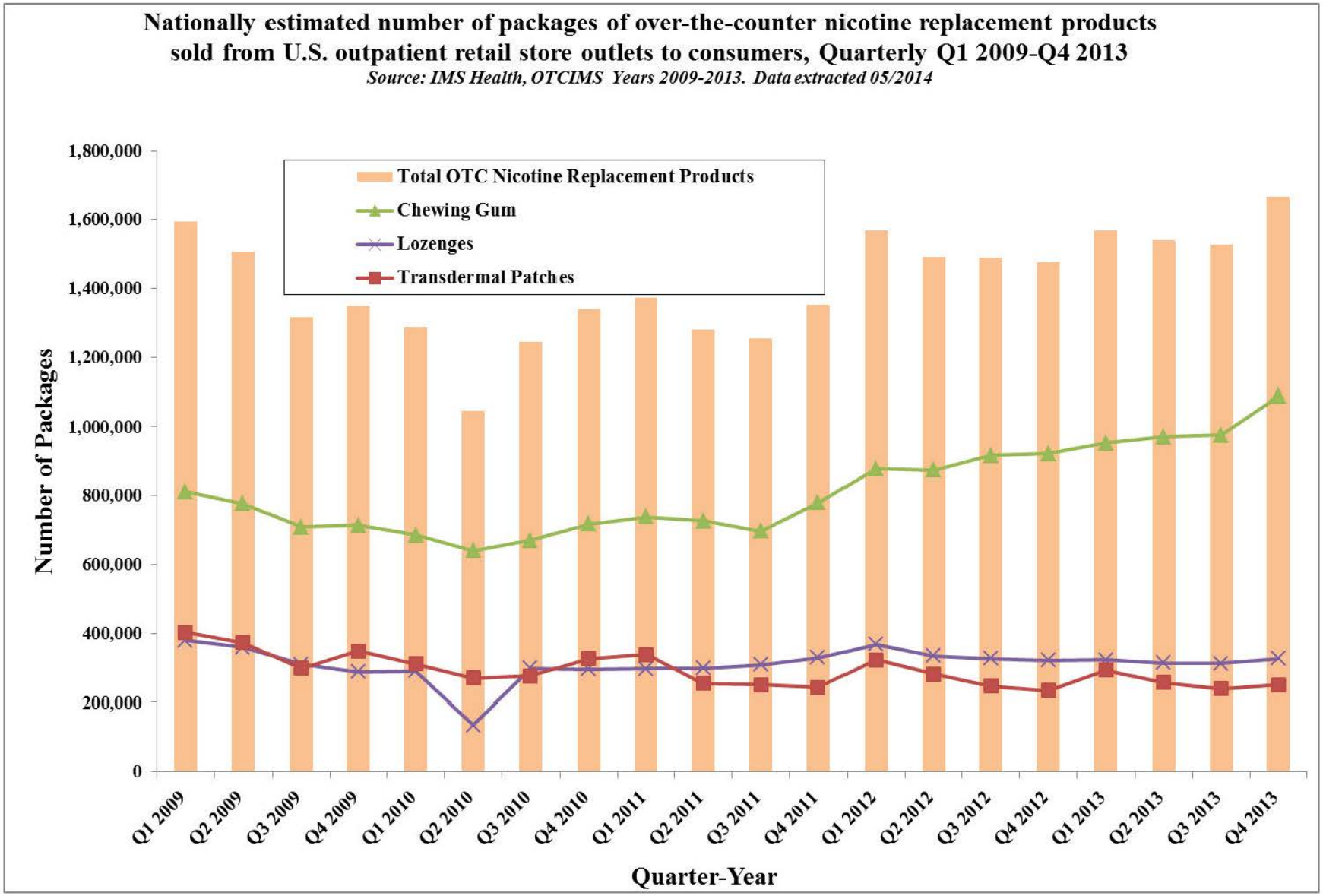
Figure 4.


Nationally estimated number of packages of over-the-counter nicotine replacement products sold from U.S. outpatient retail store outlets to consumers, Quarterly Q1 2009-Q4 2013
Source: IMS Health, OTCIMS Years 2009-2013. Data extracted 05/2014
Total OTC Nicotine Replacement Products
Chewing Gum
Lozenges
Transdermal Patches
Number of Packages
1,800,000
1,600,000
1,400,000
1,200,000
1,000,000
800,000
600,000
400,000
200,000
0
Q1 2009
Q2 2009
Q3 2009
Q4 2009
Q1 2010
Q2 2010
Q3 2010
Q4 2010
Q1 2011
Q2 2011
Q3 2011
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Q1 2012
Q2 2012
Q3 2012
Q4 2012
Q1 2013
Q2 2013
Q3 2013
Q4 2013
Quarter-Year

APPENDIX 2: Drug Use Database Descriptions.

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

IMS Health, National Prescription Audit

The National Prescription Audit (NPA™) has been the industry standard source of national prescription activity since 1952. NPA measures the "retail outflow" of prescriptions, or the rate at which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions in the United States. The NPA audit measures both what is prescribed by the physician and what is dispensed by the pharmacist. Data for the NPA audit is a national level estimate of the drug activity from retail pharmacies.

IMS, Vector One®: Total Patient Tracker (TPT)

The IMS, Vector One®: Total Patient Tracker is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting over time.

TPT derives its data from the Vector One® database which integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 1.9 billion prescription claims per year, representing over 158 million unique patients. Since 2002 Vector One® has captured information on over 15 billion prescriptions representing over 356 million unique patients.

OTC International Market Tracking (OTCIMS)

The OTC International Market Tracking (OTCIMS) platform can provide the FDA with highly accurate retail sales data for all OTC drugs. OTCIMS tracks key molecular data characteristics, strength of active ingredients; dosage form; and size of drug products by mL, number of tablets/ capsules, and/or total doses available. OTCIMS data is delivered quarterly in CD format and accessible through a secure, stand-alone desktop application called Dataview™.

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/s/

RAJDEEP K GILL
09/22/2014

HINA S MEHTA
09/22/2014

JUDY A STAFFA
09/22/2014

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

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology Review (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

Epidemiology: Review of labeling supplement regarding neuropsychiatric events associated with varenicline

Date:	September 12th 2014
Reviewer(s):	Chih-Ying Chen, Ph.D. Division of Epidemiology II
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Drug Name(s):	Varenicline (Chantix)
Subject:	Labeling supplement regarding neuropsychiatric events associated with varenicline
Application Type/Number:	NDA 21-928
Submission Number:	036
Applicant/sponsor:	Pfizer
OSE RCM #:	2014-749

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EXECUTIVE SUMMARY

Varenicline was approved under the trade name of Chantix as an aid to smoking cessation treatment for adults in May 2006. In February 2009, FDA requested that the sponsor add to the varenicline label additional warnings and precautions regarding neuropsychiatric events including, but not limited to, depression, suicidal ideation and behavior, which had been reported during post approval use of varenicline. Due to the potential seriousness of these events, FDA requested the addition of a boxed warning based on the accrual of postmarketing reports of neuropsychiatric events since approval of the drug.

In April 2014, the sponsor submitted a labeling supplement including meta-analyses of clinical data for varenicline, a literature review of observational and clinical studies, and proposed labeling revisions. The sponsor proposed revisions to the Warnings and Precautions section of the package insert (PI) regarding the risk of neuropsychiatric events with varenicline (b) (4). The Division of Anesthesia, Analgesia and Addictive Products (DAAAP) consulted the Division of Epidemiology II (DEPI II) to review the observational studies submitted by the sponsor and to determine if they support modification of the current warning on neuropsychiatric adverse events (AE).

The sponsor identified five observational studies on varenicline's neuropsychiatric risk (four publications and one unpublished study), including three which examined the association between varenicline and risk of neuropsychiatric hospitalizations, and two which investigated the association between varenicline and risk of suicide, non-fatal self-harm and initiation of an antidepressant. All the reviewed observational studies used population-level data reflecting the real-world smoking cessation drug user population. Their inclusion of patients with neuropsychiatric history extends the generalizability of the findings, because that population was excluded in most clinical trials conducted to date. The studies also all attempted to control for confounding by employing appropriate design and analytical approaches. Nonetheless, due to the due to 1) concerns about the examined outcomes and outcome measure validity, 2) using bupropion (another smoking cessation drug with risk of neuropsychiatric events) as a reference, 3) channeling bias and residual confounding between varenicline users and nicotine replacement therapy (NRT) users, and 4) limited statistical power, evidence from the observational studies reviewed is of insufficient quality to either rule in or rule out an increased risk of suicide, non-fatal self-harm, or neuropsychiatric hospitalizations associated with varenicline use. While these studies appear reassuring, they do not adequately measure the effect of Chantix on the risk of neuropsychiatric adverse events of concern and therefore cannot be interpreted to mean that there is no increased risk of neuropsychiatric events with Chantix.

DEPI II does not recommend including the findings of the five observational studies (b) (4), due to the limitations of those studies that were addressed in this review. We also (b) (4), which is not supported by currently available observational data. Given that the sponsor is conducting a Phase IV trial to examine varenicline's neuropsychiatric safety, it might be more reasonable to discuss the decision (b) (4) after the completion of the trial (the target completion date is August 2016), when further information regarding varenicline's neuropsychiatric risk is available. Alternatively, DEPI-II can suggest language for including observational studies (b) (4) which includes the appropriate interpretation of the studies' findings.

1 INTRODUCTION

Varenicline was approved under the trade name of Chantix as an aid to smoking cessation treatment for adults in May 2006. In February 2009, FDA requested that the sponsor add to the varenicline label additional warnings and precautions regarding neuropsychiatric events including, but not limited to, depression, suicidal ideation and behavior, which had been reported during post approval use of varenicline. Due to the potential seriousness of these events, FDA requested the addition of a boxed warning based on the accrual of postmarketing reports of neuropsychiatric events since approval of the drug.

In April 2014, the sponsor submitted a labeling supplement with data from clinical and observational studies for varenicline and proposed revisions to the Warnings and Precautions section of the PI regarding the risk of neuropsychiatric events with varenicline (b) (4). The Division of Anesthesia, Analgesia and Addictive Products (DAAAP) consulted the Division of Epidemiology II (DEPI II) to review the observational studies submitted by the sponsor and determine if they support modification of the current warning on neuropsychiatric adverse events (AE).

2 REVIEW MATERIALS

- Sponsor's clinical overview
- The proposed labeling changes
- Five observational studies on varenicline's neuropsychiatric risk cited in the clinical overview

3 REVIEW RESULTS

The sponsor identified five observational studies on varenicline's neuropsychiatric risk (four publications[1-4] and one unpublished study[5]). The design, data sources, methods, and main findings of each study are summarized in Appendix Table 1, Appendix Table 2 and Appendix Figure 1. The five reviewed studies include three which examined the association between varenicline and risk of neuropsychiatric hospitalizations[2;3;5] (see Section 3.1), and two which investigated the association between varenicline and risk of suicide, non-fatal self-harm and initiation of an antidepressant[1;4] (see Section 3.2).

3.1 VARENICLINE AND NEUROPSYCHIATRIC HOSPITALIZATIONS

All three studies that examined the association between varenicline and neuropsychiatric hospitalizations are retrospective cohort studies. Two of the three studies were sponsored by FDA; one was conducted by the Department of Veterans Affairs' (VA) Center for Medication Safety (unpublished)[5], and the other by the Department of Defense's U.S. Army Medical Command's Pharmacovigilance Center, described in the publication by Meyer et al.[2]. The third study was sponsored by the Danish Medical Research Council, described in the publication by Pasternak et al.[3].

The VA study[5] evaluated the incidence of neuropsychiatric hospitalizations among veterans using varenicline or nicotine replacement therapy (NRT). Patients starting varenicline or NRT between May 1, 2006 and September 30, 2007, but with no varenicline or NRT use in the previous year, were selected and matched in a 1:1 ratio by use of propensity scores (reflecting demographic characteristics, comorbidities, and psychiatric history). The study's main outcome was 30-day risk of psychiatric hospitalization, with a coded primary discharge diagnosis for one of a number of psychiatric conditions (Appendix Table 1). The study population included 14,131 varenicline users and an equal number of NRT users. Among these patients, there were 16 psychiatric hospitalizations in varenicline-treated patients, and 21 in NRT patients. No statistically significant difference was found in the 30-day risk of neuropsychiatric hospitalization for Varenicline users compared to NRT users (hazard ratio [HR] for varenicline/NRT = 0.76; 95% confidence interval [CI] 0.40-1.46). The trend was the same in the analyses using time periods longer than 30 days after a prescription fill. Similar findings were reported in a prevalent user cohort of patients who had used NRT in the past before initiating varenicline or refilling an NRT prescription.

The study by Meyer et al.[2] compared the rates of hospitalizations for neuropsychiatric adverse events among new users of varenicline and the NRT patch who started therapy between August 1, 2006 and August 31, 2007 in the Military Health System. Varenicline users were matched using propensity scores to NRT users, with subgrouping by concomitant use of the prescription smoking cessation drug bupropion, or a history of neuropsychiatric disease. After propensity score matching, there were 11,978 varenicline users and an equal number of NRT users in the study sample. The main outcome was a primary hospital discharge diagnosis for one of a number of neuropsychiatric condition (Appendix Table 1) within 30 days of drug initiation. In the study's propensity score matched samples, there were 16 psychiatric hospitalizations among varenicline users and 14 among NRT users. No statistically significant difference was found with respect to the risk of neuropsychiatric hospitalization comparing varenicline users to NRT users (HR 1.14; 95% CI 0.56-2.34). HRs were reduced further among patients without exposure to concomitant bupropion (HR = 0.70; 95% CI 0.27-1.84) or a history of neuropsychiatric disease (HR = 0.80; 95% CI 0.21-2.98). The trend was the same when patients were followed 60 days after drug initiation. Finding was similar when using any inpatient diagnosis as the outcome measure (HR 0.79, 0.50-1.24). The HR estimate was within the range reported for the main outcome, but indicating a lowered risk of outpatient neuropsychiatric visits (HR 0.71, 0.60-0.84) for varenicline users compared to NRT users.

The study by Pasternak et al.[3] compared the rates of emergency department visit or hospital admission with one of a number of psychiatric diagnoses (Appendix Table 1) that had occurred within 30 days of treatment initiation among new users of varenicline and bupropion who started therapy between January 1st 2007 and December 31 2010 in Denmark. Overall, 59,790 new users of varenicline and 17,936 new users of bupropion were identified. In this unmatched cohort, the distribution of baseline characteristics was generally similar between the two groups. To further control for confounders, 17,935 varenicline users were matched 1:1 to bupropion users. A total of 85 psychiatric events occurred. There were 39 (0.22%) psychiatric adverse events among17,935 varenicline users (rate 27 events per 1000 person-years) and 46 (0.26%) events among 17,935 bupropion users (rate 31 per 1000). There were three cases of suicide attempt or completed suicide among varenicline users and one case among bupropion users. There was no significant association between varenicline use and psychiatric adverse events compared with bupropion use (HR: 0.85. 95% CI: 0.55- 1. 30; Table 2). The risk of psychiatric events associated with varenicline compared with bupropion appeared lower in participants without a history of psychiatric disorder than in participants with a history, although this was based on few cases, and the difference in risk of psychiatric events associated with varenicline versus bupropion by history of psychiatric disorder was not statistically significant (P=0.12).

3.2 VARENICLINE AND SUICIDE RELATED OUTCOMES

The two studies that examined varenicline and suicide related outcomes (Gunnell et al. and Thomas et al.) were both conducted by researchers at the University of Bristol and were based on the same data source (the General Practice Research Database [GPRD], subsequently known as the Clinical Practice Research Datalink [CPRD]), per a grant received from the Medicines and Healthcare products Regulatory Agency (MHRA).[1;4]

The earlier study by Gunnell et al.[1] examined the 3-month risk of suicide, non-fatal self-harm and the initiation of antidepressants in 10,973 varenicline users, 6,422 bupropion users and 63,265 NRT users who received a prescription between September 01 2006 and May 31 2008. In multivariate analyses, no association was found for varenicline versus NRT with respect to self-harm (HR: 1.12, 95% CI: 0.67-1.88) or the initiation of antidepressants (HR: 0.88, 95% CI: 0.77-1.00). Two suicides were identified both within the NRT group, from the death details and postmortem findings recoded on GPRD. It should be noted that a previous study using the GPRD to determine the incidence of suicide among asthma patients yielded a rate below that of the general population, suggesting under-ascertainment of suicide.[6]

Thomas et al.[4] examined the 3-month risk of suicide-related outcomes and all-cause mortality in 31,260 varenicline users, 6,741 bupropion users and 81,545 NRT users who received their first prescription between September 01 2006 and October 31 2011. Ninety-two cases of suicide and non-fatal self-harm were identified from the linked UK CPRD, Office for National Statistics (ONS) mortality data and Health Episode Statistics (HES) data during 3 months of follow-up after the date of treatment initiation: 69 among NRT users, 4 among bupropion users and 19 among varenicline users. Comparing varenicline users to NRT users, the multivariate-adjusted HR for fatal and non-fatal self-harm included the null (HR=0.88, 0.52 to 1.49), but showed a lower risk of initiation of antidepressants (HR= 0.75, 0.65 to 0.87) and all-cause mortality (0.44, 0.30-0.63). Similar findings were reported using propensity score methods, but the direction of risk estimate changed in the instrumental variable analyses (See section 4.2 for further discussions). The trend did not change in most of the sensitivity analyses that extended the follow-up to 6-, or 9-months, as well as restricting to first-time users of smoking cessation drugs.

4 DISCUSSION

The five observational studies all used population-level data reflecting the real-world smoking cessation drug user population. The inclusion of patients with neuropsychiatric history extends the generalizability of the findings, because that population was excluded in most clinical trials conducted to date. They also all attempted to control for confounding by employing appropriate design and analytical approaches. Nonetheless, these studies themselves were not able to provide conclusive evidence with regard to the risk of neuropsychiatric adverse events associated with varenicline. We will address the specific limitations of the existing observational studies in the following sections.

4.1 CONCERNS REGARDING THE EXAMINED OUTCOMES AND VALIDITY OF OUTCOME MEASURES

The outcomes of interest in the existing studies—suicide, self-harm, neuropsychiatric hospitalizations, and initiation of antidepressants (used as a proxy for incident depression), although clinically meaningful, only capture some of the neuropsychiatric adverse events[1] that have been reported in association with varenicline use to FDA's adverse event reporting system. Moreover, all reviewed studies relied on diagnostic codes (ICD-9, ICD-10 or Read codes, etc.) to ascertain outcomes. We are concerned that diagnostic codes cannot accurately capture all the serious neuropsychiatric adverse events that have been associated with varenicline. Such events involve abrupt behavioral and/or mood changes, which are difficult to accurately translate into a medical coding system, and may result in patient contact with legal, rather than medical, systems. Without a detailed exploration of medical charts to identify all the codes that might be used to capture these outcomes, as well as patient and provider interviews to determine behavior and coding practices, it is not possible to estimate how many events were missed in those studies. Such problems are inherent to the study of behavioral and psychiatric outcomes, which present different challenges than studying purely medical events.

Additionally, it is difficult to interpret the findings on the outcomes that were captured. First, none of the reviewed studies reported the validity of the chosen codes. Only one study[3] reported some measure of validity for some of the ICD-10 codes used to identify their outcomes[2]. In the studies that examined the

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[a] There have been post marketing reports of neuropsychiatric symptoms, some serious, including changes in mood, agitation, psychosis, hallucinations, paranoia, delusions, homicidal ideation, hostility, changes in behavior, anxiety, panic, suicidal ideation, suicide attempt and completed suicide in patients attempting to quit smoking with varenicline.

[2] Pasternak et al. had reported high positive predictive value (>90%) for the ICD-10 codes used to identify a schizophrenia-spectrum disorder and a single depressive episode. However, the two conditions are only some of several psychiatric adverse events that the study targeted.

association between varenicline and neuropsychiatric hospitalizations, clinically important psychiatric events that did not include hospitalization (such as a successful suicide without hospitalization) were not captured[2;3;5]. Although the Meyer et al. study[2] also examined a secondary outcome that included outpatient visits with a neuropsychiatric diagnosis, this metric may be simply capturing pre-existing psychiatric comorbidities, rather than treatment emergent psychiatric events. Moreover, a psychiatric episode resulting in discontinuation of smoking cessation drugs without a health care professional encounter would be missed; in light of the stigma that can be attached to psychiatric diagnoses in medical records, particularly in the military, this possibility cannot be ruled out.

Under-ascertainment of outcomes is also a concern with respect to the studies that examined the association between varenicline and suicide/non-fatal self-harm.[1;4] In fact, the Read codes used by GPRD/CPRD have been shown to be unreliable for detecting suicide, and under-report non-fatal self-harm, which undermines the inferential capacity of the Gunnell study because it solely used Read codes to investigate suicide/non-fatal self-harm risk associated with varenicline. We have more confidence in the event count of suicide deaths observed in the Thomas et al. study, because the investigators linked CPRD records to the U.K. mortality data to capture this outcome. The incidence of suicide in the Thomas et al. study's cohort of smokers (27.4 per 100,000 person-years) is about three times the rate obtained from the general CPRD population (9.4 per 100 000 person-years)[10], which is consistent with findings from prior research that have shown a twofold to threefold higher risk of suicide in smokers versus non-smokers.[11;12] However, Thomas et al. did not compare the rate of suicide deaths among Chantix users to users of another smoking cessation product to obtain a Chantix-associated risk estimate for suicide death. Rather, they compared the rate of suicide death or attempted suicide, a composite outcome, between Chantix users and users of another smoking cessation product. Similar to neuropsychiatric medical encounters, we are concerned about the undercounting of suicide attempts due to the stigma that can be attached to such diagnoses, the difficulty in determining intentionality of injury, and the fact that such attempts are not always brought to medical attention.

Lastly, in the studies that examined the risk of antidepressant initiation,[1;4] prescribing of antidepressants was not a specific measure of incident depression, since antidepressants are also used to treat other disorders, including nonpsychiatric indications.

4.2 OTHER DESIGN AND METHODOLOGICAL ISSUES

The study by Pasternak et al. compared risk of neuropsychiatric emergency department visits or hospitalizations between varenicline users and bupropion users; the study found a non-significant 15% lowered risk associated with varenicline use compared with bupropion use (HR: 0.85. 95% CI: 0.55- 1.30; Appendix Table 2, Appendix Figure1). However, given that bupropion also has been associated with psychiatric adverse events and carries a boxed warning alerting about this possiblity,[13;14] this finding does not provide reassurance of varenicline's neuropsychiatric safety.

The study by Thomas et al. included data from the timeframe after the publicity of varenicline's neuropsychiatric safety concerns. Adverse publicity may have resulted in patients with a history of neuropsychiatric illness being preferentially prescribed NRT, and healthier patients being preferentially prescribed varenicline (i.e., channeling bias). In fact, varenicline users in the study were indeed less likely to have a history of chronic diseases and psychiatric illness, and had a lower frequency of previous use of hypnotics, antipsychotics, and antidepressants.

After adjusting for baseline characteristics, the all-cause mortality risk at 3 months appeared to be significantly lower among varenicline users than NRT users in two of the three analyses conducted in the Thomas et al. study. The hazard ratio (HR) of 3-month all-cause mortality comparing varenicline to NRT was 0.44 in the Cox regression analysis, and 0.37 in the Propensity score matching analysis (Table 1), which translated to an adjusted risk difference of -1.4 to -2 per 1,000 patients (Table 1 and see the calculation from HRs to risk differences in Appendix I). Given that three months is too short a timeframe

for realizing the survival benefits of smoking cessation, the reduced risk in all-cause mortality most likely reflects the generally healthier varenicline users than NRT users. Therefore, the risk estimates of the primary outcome (i.e., 3-month suicide and non-fatal self-harm) from those two analyses would likely carry the impact of the residual baseline differences. Their third analysis using an instrumental variable (IV) approach appeared to reduce the impact of residual confounding, because the difference in 3-month mortality risk between varenicline and NRT users became smaller (-0.8 per 1,000 patients, Table 1). IV methods also resulted in a slight increase in 3-month fatal/non-fatal self-harm comparing varenicline users to NRT users (risk difference: 0.4 [95% CI: -0.8-1.5] per 1,000 patients). The change in direction of the risk estimate (from a negative difference to a positive difference) for the primary outcome raise the concern that varenicline use could increase risk of fatal/non-fatal self-harm. Although the observed risk difference is numerically small, it is worth-noting that the possible under-ascertainment of fatal/non-fatal self-harm (as mentioned in section 4.1) would lead to an under-estimate of the risk difference. Nevertheless, given that the risk estimate was not statistically significant, the finding cannot be used to either rule in, or rule out, an association between varenicline use and fatal/non-fatal self-harm.

Table 1 Findings from the Thomas et al. study

	Risk estimate (95% Confidence interval) (Reference: NRT users)	
Analytical approaches	3-month suicide and non-fatal self-harm	3-month all-cause mortality
Cox regression analyses	HR: 0.88 (0.52-1.49) Risk difference per 1,000: -0.1[†]	HR: 0.44* (0.30-0.63) Risk difference per 1,000: -1.4 ~-2[†]
Propensity score matching analyses	HR: 0.87 (0.51-1.48) Risk difference per 1,000: -0.1[†]	HR: 0.37* (0.26-0.53) Risk difference per 1,000: ~-2[†]
Instrumental variable analyses	Risk difference per 1,000: 0.4 (-0.8-1.5)	Risk difference per 1,000: -0.8 (-2.8-1.1)

HR: Hazard ratio
*p value < 0.05.
[†] see the calculation from HRs to risk differences in Appendix I

5 CONCLUSION

Although none of the reviewed observational studies found differences in the risk of serious neuropsychiatric events between varenicline and the reference drug (NRT or bupropion) users, all studies had a number of study design limitations. Most importantly, the outcomes examined in these studies did not cover the full range of the neuropsychiatric adverse events that have been seen in postmarketing spontaneous adverse event reports associated with varenicline. These limitations may underestimate the actual incidence of neuropsychiatric adverse events, and restrict our ability to predict the direction of the relative risk associated with varenicline. Therefore, while these studies appear reassuring, they do not adequately measure the effect of Chantix on the risk of neuropsychiatric adverse events of concern and therefore cannot be interpreted to mean that there is no increased risk of neuropsychiatric events with Chantix.

6 RECOMMENDATIONS

The sponsor proposed two main changes to the label: 1) Describing findings of (b) (4) observational studies in the Warnings and Precautions section (b) (4)

DEPI II does not recommend including the findings of the five observational studies as currently proposed in the label revision, due to the limitations of those studies that were addressed in this review. We also (b) (4) . Given that the sponsor is conducting a

Phase IV trial to examine varenicline's neuropsychiatric safety, it might be more reasonable to discuss the decision (b) (4) after the completion of the trial (the target completion date is August 2016), when further information regarding varenicline's neuropsychiatric risk is available. Alternatively, DEPI-II can suggest language for including observational studies (b) (4) which includes the appropriate interpretation of the studies' findings.

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APPENDICES

Table 1 Design and methods of the observational studies on varenicline use and neuropsychiatric risk

	The VA Study (unpublished)	**Meyers et al.**	**Pasternak et al.**	**Gunnel et al.**	**Thomas et al.**
Design	Retrospective cohort study	Retrospective cohort study	Retrospective cohort study	Retrospective cohort study	Retrospective cohort study
Time frame	May 01 2006 to Sep 30 2007	Aug 01 2006 to Aug 31 2007	Jan 1 2007 to Dec 31 2010	Sep 01 2006 to May 31 2008	Sep 01 2006 to Oct 31 2011
Data sources	VA health care data bases (claims and administrative data)	Military health system data (Claims and administrative data)	Nation-wide linked health care data in Denmark including information on prescription drug use, emergency department visit, hospital admission, neuropsychiatric diagnosis, etc.	UK General Practice Research Database (GPRD), subsequently known as the Clinical Practice Research Datalink (CPRD) (Electronic health care records including demographic, consultation, prescribing, referral and health outcome data from ~500 General Practices)	UK CPRD linked to Office for National Statistics (ONS) mortality data and Health Episode Statistics (HES) data
Exposure	Varenicline or NRT	Varenicline or NRT	Varenicline or bupropion	Varenicline, bupropion, or NRT	Varenicline, bupropion, or NRT
Reference group	NRT	NRT	Bupropion	NRT	NRT

Main Outcomes	30-day Neuropsychiatric hospitalizations
	• hospitalization with a primary discharge diagnosis from among the ICD-9 codes of the following conditions:
	  • Comprehensive mental health disorders
	  • Acute composite
		30-day Neuropsychiatric hospitalizations
		• Primary definition: hospitalization with a primary discharge diagnosis from among the ICD-9 codes of the following conditions:
		  • Drug-induced mental disorders
			30-day Neuropsychiatric emergency department visits or hospitalizations with a primary diagnosis of the following diagnosis identified using ICD-10 codes
			• Mood disorder
			• Psychotic disorder
			• Substance abuse
				90-day Suicide, non-fatal self-harm*, depression, all-cause mortality
				• Suicide, non-fatal self-harm and all-cause mortality were identified by relevant diagnoses codes (Read codes) and Oxford Medical
					90-day Suicide, non-fatal self-harm, depression, all-cause mortality
					• Suicide was defined as death from suicide in the ONS mortality database, using ICD-10 codes of intentional self-harm and

	mental health disorders • Depression • Schizophrenia • Bipolar disorder • Suicide attempt • Psychosis excluding bipolar, depression and schizophrenia	• Transient mental disorders • Schizophrenia • Episodic and mood disorders • Delusional disorders • Other nonorganic psychoses • Anxiety disorders • Personality disorders • Posttraumatic stress disorder (PTSD) • Depressive disorders • Suicide attempt. • Secondary definition: hospitalization with a neuropsychiatric condition in any discharge diagnoses, or, any neuropsychiatric diagnoses in outpatient records that occurred twice on different days	• Neurotic, stress-related or somatoform disorder • Behavioral syndromes associated with physiological disturbances and physical factors, disorders of adult personality and behavior • unspecified mental disorder, confusion, hallucinations, • symptoms and signs involving emotional state and symptoms and signs involving appearance and behavior	Information System (OXMIS) medical terms. • No death certificates were obtained for any deaths. • Depression was defined as the initiation of antidepressant therapy and excluded patients who had been prescribed antidepressants at any time in the six months before starting smoking cessation therapy	undetermined deaths • Non-fatal self-harm was identified from hospital admission for self-harm from the HES data • Depression was defined as the initiation of antidepressant therapy
Study population	Primary: New users of varenicline or NRT (no smoking cessation medicine for 12 months) during the study timeframe and matched in a 1:1 ratio by propensity scores	New users (17+ years-old) of varenicline and NRT patch (no smoking cessation medicine for 6 months) during the study time frame and matched 1:1 by propensity scores	New users (18+ years-old) of varenicline and bupropion during the study time frame and matched 1:1 by propensity scores	Users (18+ years-old) of varenicline, bupropion, or NRT during the study timeframe	Primary: New users (18+ years-old) of varenicline, bupropion, and NRT (no smoking cessation medicine for 12 months) during the study timeframe

	Secondary: Prevalent users of NRT who initiated varenicline or continue on NRT during the study timeframe, matched on 1:2 ratio by propensity score				Secondary: First-time users of varenicline, bupropion and NRT during the study timeframe (no prior use of smoking cessation medicines in the database)
Follow-up	Follow-up continued for 30 days after this prescription with censoring for death, end of study periods or event, whichever came first	Follow-up continued for 30 days after this prescription with censoring for deployment, stationing overseas, loss of MHS eligibility, death or event, whichever came first	Follow-up started from the date when the first prescription was filled and censored at the respective date of death, disappearance, immigration, end of study (31 December 2010), switching to the other study drug or psychiatric adverse event, whichever occurred first	Follow-up continued for 90 days after first prescription with censoring for death, starting another smoking cessation drugs, left the practice, primary event (suicide or non-fatal self-harm), whichever came first	Follow-up continued for 90 days after first prescription with censoring for death, left the practice, primary event (suicide or non-fatal self-harm), end of study period, whichever came first
Analyses	Cox proportional-hazards regression	Cox proportional-hazards regression	Cox proportional-hazards regression	Cox proportional-hazards regression	Cox proportional-hazards regression Propensity score matching and Cox proportional-hazards regression Instrumental variable analysis

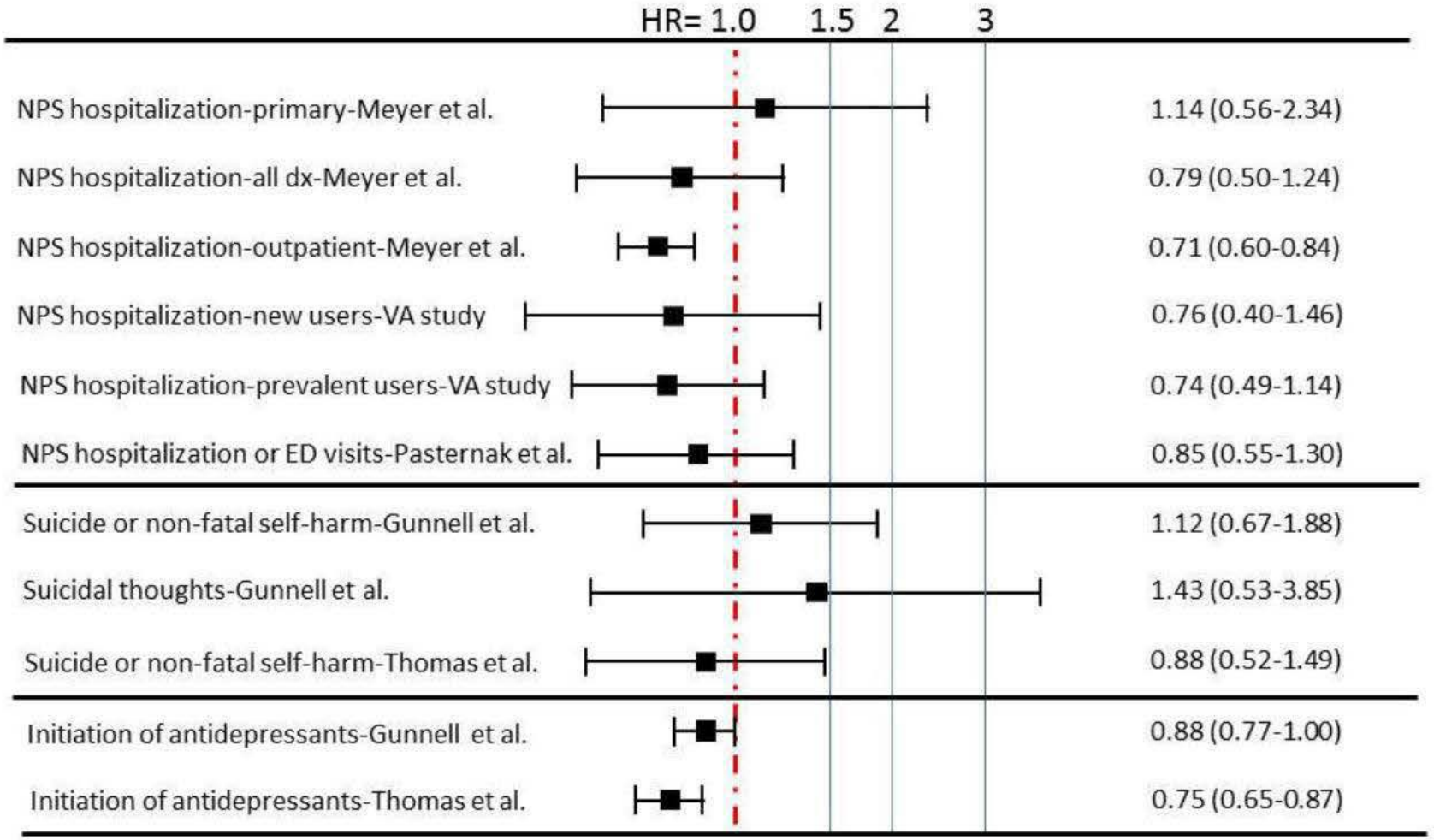
*Non-fatal self-harm: suicide attempt that did not result in death

Table 2 Main study findings of the observational studies on varenicline' s neuropsychiatric risk

Study	Outcome	Analyses	Varenicline (N event/total/IR*)	Reference group		Fully-adjusted Hazard Ratio
				NRT (N event/total/IR*)	Bupropion (N event/total/IR*)	
Meyer et al. 2013	NPS hospitalization (primary diagnosis) in 30 days	New users, PS-matched	16/10,814/18	14/10,814/16	-	1.14 (0.56-2.34)
Meyer et al. 2013	NPS hospitalization (any diagnosis) in 30 days	New users, PS-matched	34/10,710/39	43/10710/49	-	0.79 (0.50-1.24)
Meyer et al. 2013	NPS Outpatients visits in 30 days	New users, PS-matched	234/10710/269	327/10710/378	-	0.71 (0.60-0.84)
VA study	NPS hospitalization (primary diagnosis) in 30 days	New users, PS-matched	16/14,131/16	21/14,131/21	-	0.76 (0.40-1.46)
VA study	NPS hospitalization (primary diagnosis) in 30 days	Prevalent users, PS-matched	29/12,258/29	94/24,185/47	-	0.74 (0.49-1.14)
Pasternak et al.	NPS emergency room visit or hospitalization in 30 days	New users, PS-matched	39/17,975/27	-	46/17,935/31	0.85 (0.55-1.30)
Gunnell et al. 2009	Suicide or non-fatal self-harm in 90 days	Prevalent users	18/10,973/5.3*	141/63,265/7.5*	-	1.12† (0.67-1.88)
Gunnell et al. 2009	Suicide thoughts in 90 days	Prevalent users	5/10,973/NA	30/63,265/NA	-	1.43† (0.53-3.85)
Thomas et al. 2013	Suicide or non-fatal self-harm in 90 days	New users	19/30,352/3	69/78,407/4	-	0.88[&] (0.52-1.49)
Gunnell et al. 2009	Initiation of antidepressants in 90 days‡	Prevalent users	292/9162/NA	1792/49415/NA	-	0.88† (0.77-1.00)
Thomas et al. 2013	Initiation of antidepressants in 90 days[¥]	New users	255/18,386/57	799/42,475/77	-	0.75[&] (0.65-0.87)

NRT: Nicotine replacement therapy; IR: Incidence Rate=event/1,000 person-year; NPS: neurologic/psychiatric; PS: propensity score
Hazard Ratios calculated using Cox proportional hazards regression model
*age and sex-standardized
†Adjusted for age; sex; use of hypnotics, antipsychotics, and antidepressants; alcohol misuse; previous suicide related event; previous smoking cessation therapy; psychiatric consultation; date of initial exposure to product, number of general practice visits per year, index of multiple deprivation, UK region.
[&]Adjusted for sex; age; previous psychiatric illness or consultation; previous use of psychotropic drugs such as hypnotics, antipsychotics and antidepressants; previous self-harm; socioeconomic position; major chronic illness; number of general practice consultations in the year before the prescription; exposure to the drug before or after 2008; year of first prescription; and previous use of a smoking cessation product.
‡Restricted to those with no antidepressants in the six months before smoking cessation therapy.
[¥]Restricted to those with no previous antidepressant use

Figure 1 Forest plot of the main study findings of the observational studies on varenicline' s neuropsychiatric risk



NPS: Neuropsychiatric; ED: Emergency department; HR: Hazard ratio

Appendix I Calculation of the risk differences of study outcomes based on the hazard ratios of the Cox regression and propensity score matching analyses of the Thomas et al. study

Fatal and non-fatal self-harm

1. **Calculate the crude outcome rates from event counts and follow-up person-time**
   NRT group =69/19196*1000 = 3.59 per 1,000 patient-year
   Varenicline group =19/7363*1000 = 2.58 per 1,000 patient-year

2. **Calculate the adjusted outcome rates from the crude outcome rates and risk ratios of COX regression or PS matching**
   -Adjusted outcome rates calculated based on the crude rate of NRT group and the HR of COX regression
   NRT group =3.59 * 1 = 3.59
   Varenicline group =3.59 * (0.88) = 3.16

   -Adjusted outcome rates calculated based on the crude rate of Varenicline group and the HR of COX regression
   Varenicline group =2.58 * 1 = 2.58
   NRT group =2.58 / 0.88 = 2.93

   -Adjusted outcome rates calculated based on the crude rate of NRT group and the HR of PS matching
   NRT group =3.59 * 1 = 3.59
   Varenicline group =3.59 * (0.87) = 3.12

   -Adjusted outcome rates calculated based on the crude rate of Varenicline group and the HR of PS matching
   Varenicline group =2.58 * 1 = 2.58
   NRT group =2.58 / 0.87 = 2.97

3. **Calculate the adjusted risk differences between varenicline and NRT reflected by the risk ratio of COX regression or PS matching**
   -Adjusted risk differences based on risk ratio of COX regression=
   3.16-3.59= -0.43 (per 1,000 patient-year)= ~-0.1 (per 1,000 patients per 3 months) **OR**
   2.58-2.93= -0.35 (per 1,000 patient-year)= ~-0.1 (per 1,000 patients per 3 months)
   -Adjusted risk differences based on risk ratio of COX regression=
   3.12-3.59= -0.47 (per 1,000 patient-year)= ~-0.1 (per 1,000 patients per 3 months) **OR**
   2.58-2.97= -0.39 (per 1,000 patient-year)= ~-0.1 (per 1,000 patients per 3 months)

Mortality

1. **Calculate the crude outcome rates from event counts and follow-up person-time**
   NRT group =292/19944*1000 = 14.64 per 1,000 patient-year
   Varenicline group =33/7575*1000 = 4.36 per 1,000 patient-year

2. **Calculate the adjusted outcome rates from the crude outcome rates and risk ratios of COX regression or PS matching**
   -Adjusted outcome rates calculated based on the crude rate of NRT group and the HR of COX regression

NRT group =14.64 * 1 = 14.64
Varenicline group =14.64 * (0.44)= 6.44

-Adjusted outcome rates calculated based on the crude rate of Varenicline group and the HR of COX regression
Varenicline group =4.36 * 1 = 4.36
NRT group =4.36 / 0.44 = 9.90

-Adjusted outcome rates calculated based on the crude rate of NRT group and the HR of PS matching
NRT group =14.64 * 1 = 14.64
Varenicline group =14.64 * (0.37)= 5.42

-Adjusted outcome rates calculated based on the crude rate of Varenicline group and the HR of PS matching
Varenicline group =4.36 * 1 = 4.36
NRT group =4.36 / 0.37 = 11.78

3. **Calculate the <u>adjusted risk differences</u> between varenicline and NRT reflected by the risk ratio of COX regression or PS matching**

-Adjusted risk differences based on risk ratio of COX regression=
6.44-14.64= -8.2 (per 1,000 patient-year)= ~-2.1 (per 1,000 patients <u>per 3 months</u>) **OR**
4.36-9.90= -5.5 (per 1,000 patient-year)= ~-1.4 (per 1,000 patients <u>per 3 months</u>)
-Adjusted risk differences based on risk ratio of PS matching=
5.42-14.64= -9.2 (per 1,000 patient-year)= ~-2.3 (per 1,000 patients <u>per 3 months</u>) **OR**
4.36-11.78= -7.4(per 1,000 patient-year)= ~-1.9 (per 1,000 patients <u>per 3 months</u>

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/s/

CHIH-YING CHEN
09/17/2014

ELIZABETH M MALONEY
09/17/2014

JUDY A STAFFA
09/18/2014

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

Provision of Pharmacovigilance Data

Date:	May 16, 2014
Reviewer:	Sara Camilli, PharmD, BCPS, Safety Evaluator Team Leader Division of Pharmacovigilance II (DPV II)
Director:	Scott Proestel, MD, Director DPV II
Product Name:	Chantix (varenicline tartrate)
Subject:	Neuropsychiatric Events Crude Counts 2008-2013
Application Type/Number:	NDA 21928
Applicant/Sponsor:	Pfizer, Inc.
OSE RCM #:	2014-749

1 INTRODUCTION

This document provides crude counts of FDA Adverse Event Reporting System (FAERS) data for domestic varenicline and neuropsychiatric event reports for 2008-2013 in support of a Center Director Briefing.

On April 8, 2014, Pfizer submitted a supplement that proposes [redacted] (b) (4) To address this proposal, a Center Director Briefing will be held on May 22, 2014, and an Advisory Committee meeting is planned for the fall of 2014. The Division of Epidemiology consulted the Division of Pharmacovigilance II (DPV II) to provide updated crude counts of FAERS data since the last review, completed in 2008, for the Center Director Briefing.

Neuropsychiatric adverse events were initially added to the Adverse Reaction section of the product labeling in November 2007. Subsequently, it was elevated to a Warning in January 2008 and a Boxed Warning in July 2009, consistent with recommendations of two DPV II reviews.[a] [b] A Risk Evaluation and Mitigation Strategy (REMS) and postmarketing study requirement for a large clinical safety trial of neuropsychiatric events were issued in May 2008. Results of the postmarketing study are expected in 2017.

2 METHODS AND MATERIALS

The FDA Adverse Event Reporting System (FAERS) was searched with the strategy described in Table 1.[c]

Table 1. FAERS Search Strategy	
Date of search	May 13, 2014
Time period of search	Event Date OR Initial Receive Date: 01/01/2008 – 12/31/2013
Active Ingredient	Varenicline, varenicline tartrate
Search Terms	See Appendix A
Country (derived)	US

3 DATA

The FAERS database received 48,200 domestic adverse event reports for varenicline from January 1, 2008, through December 31, 2013. Of the 48,200 reports, 17,739 (37%) were neuropsychiatric adverse event reports, of which 572 (3%) reported a fatal outcome.

[a] Pollock M, Mosholder A. Psychiatric events (including suicides) associated with varenicline and bupropion. December 8, 2008. OSE RCM# 2008-1291.

[b] Pollock M, Mosholder A. Suicidality associated with varenicline, bupropion, and nicotine transdermal patch. July 16, 2008. OSE RCM #2007-2425.

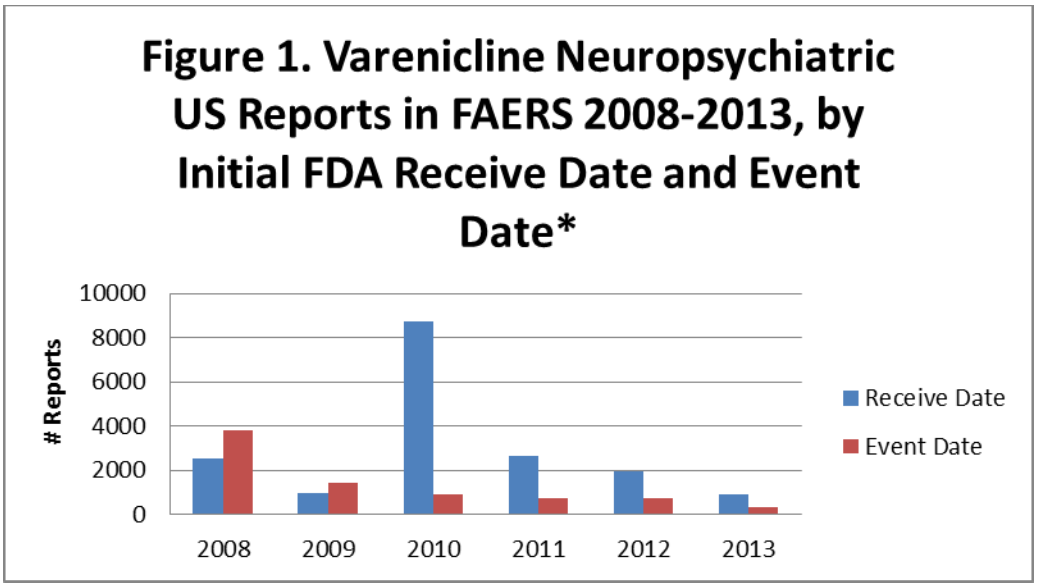
[c] FAERS is a database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. FAERS data do have limitations (e.g., variable quality and quantity of information provided, cannot determine causality, voluntary reporting system, reporting biases). Additionally, FAERS cannot be used to calculate the incidence of an adverse event in the U.S. population. FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

Table 2 and Figures 1 - 3 provide crude counts of domestic neuropsychiatric adverse event reports in FAERS for 2008 through 2013. The data is provided by initial receive date and event date. FDA received a bolus of reports in 2010 that corrected a submission error of Pfizer's periodic reports. Therefore, looking at trends in the reports by event date may provide a more accurate picture of the adverse events over time. A limitation of trending reports by event date is that all reports will not be captured, as event date may not be reported or may be prior to the time period of interest. Of the 17,739 neuropsychiatric reports received from 2008 to 2013 for varenicline, 12,176 (69%) provided an event date, of which 4,420 (36%) occurred prior to 2008.

The FAERS data shows that FDA continues to receive reports of neuropsychiatric events associated with varenicline. Numbers of reports for all types of neuropsychiatric events declined from 2008 through 2013. Figure 4 provides crude level data for fatal neuropsychiatric events, which has also declined over time.

Table 2. FAERS Crude Counts for Varenicline and Neuropsychiatric Events U.S. Reports 2008-2013

Year	FDA Initial Receive Date					Event Date				
	All	Suicid-ality	Psychosis/ Mania	Aggression/ Violence	Misc. Neuropsych	All	Suicid-ality	Psychosis/ Mania	Aggression/ Violence	Misc. Neuropsych
2008	2555	969	524	682	2210	3798	1634	584	917	3272
2009	989	376	246	288	792	1424	791	291	430	1180
2010	8716	2353	892	1426	8189	899	222	157	169	767
2011	2637	1497	481	868	2442	737	129	97	149	622
2012	1946	453	239	369	1820	755	87	81	119	673
2013	896	208	75	144	680	364	57	28	68	316
Total	**17739**	**5856**	**2457**	**3777**	**16133**	**7977**	**2920**	**1238**	**1852**	**6830**



*Of the 17,739 neuropsychiatric reports received from 2008 to 2013 for varenicline, 12,176 (69%) provided an event date, of which 4,420 (36%) occurred prior to 2008.

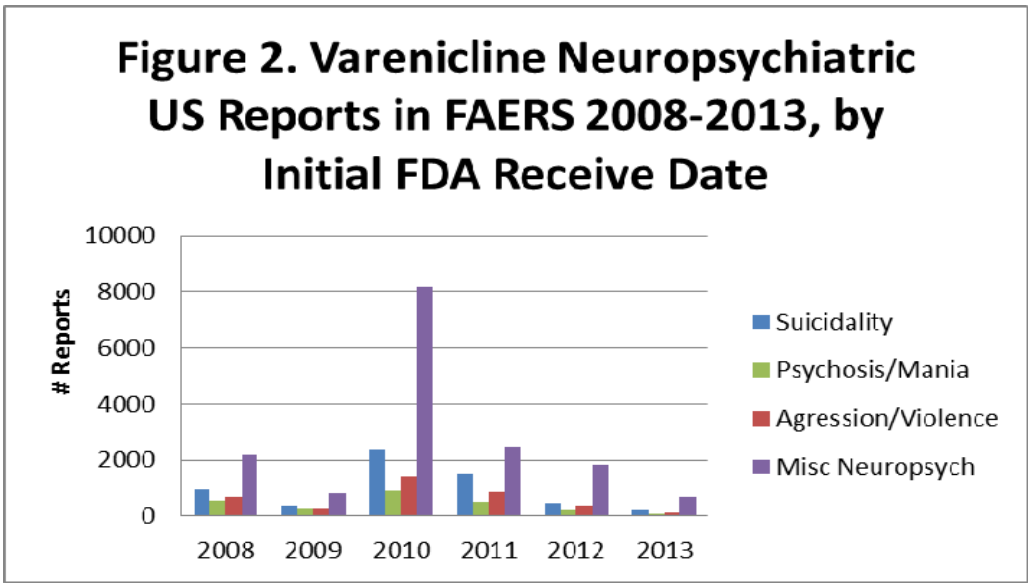


Figure 2. Varenicline Neuropsychiatric US Reports in FAERS 2008-2013, by Initial FDA Receive Date
Reports
10000
8000
6000
4000
2000
0
2008
2009
2010
2011
2012
2013
Suicidality
Psychosis/Mania
Agression/Violence
Misc Neuropsych

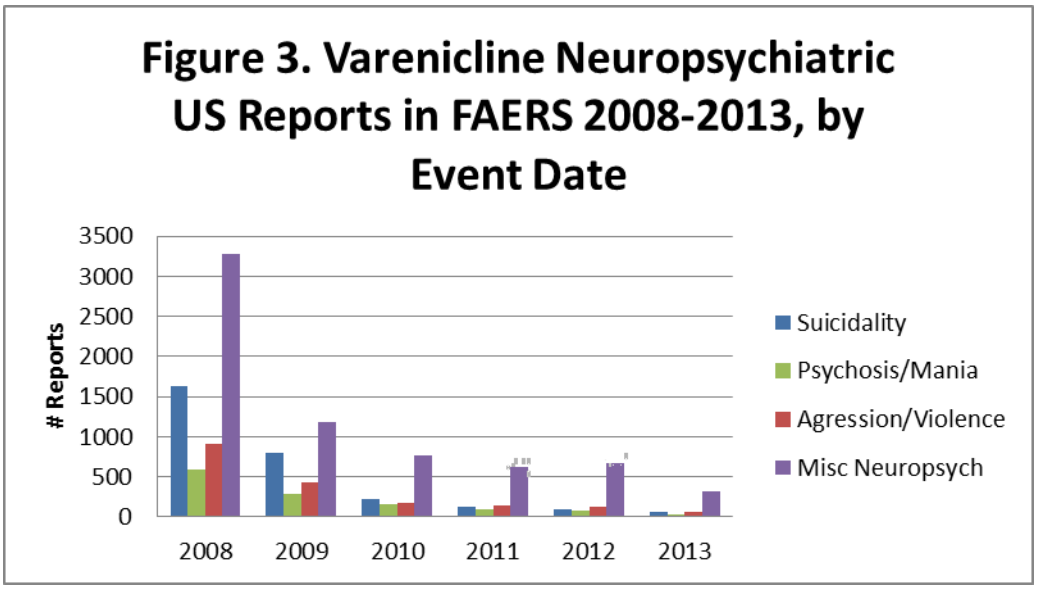
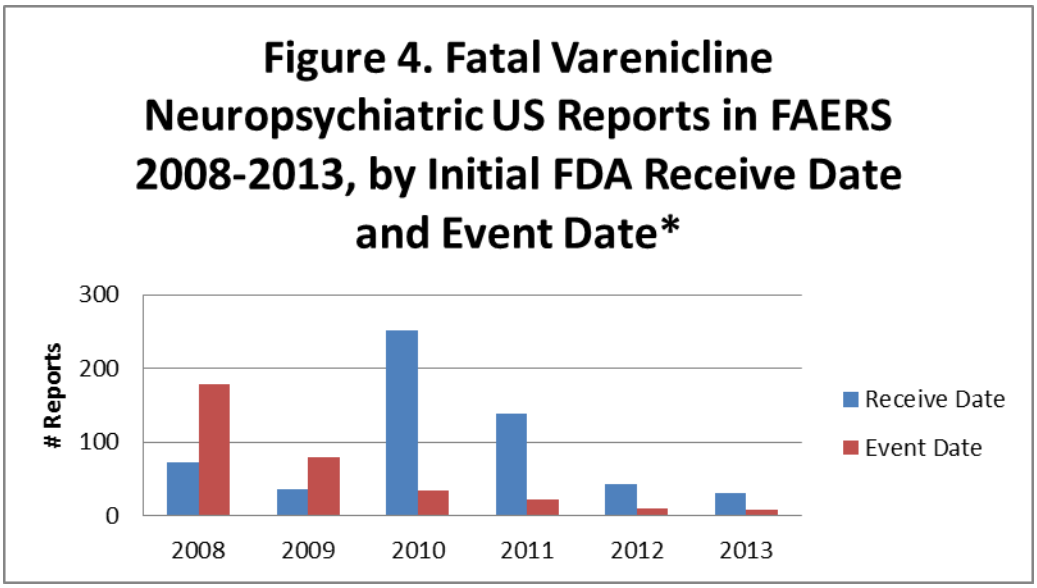


Figure 3. Varenicline Neuropsychiatric US Reports in FAERS 2008-2013, by Event Date
Reports
3500
3000
2500
2000
1500
1000
500
0
2008
2009
2010
2011
2012
2013
Suicidality
Psychosis/Mania
Agression/Violence
Misc Neuropsych



*Of the 572 fatal neuropsychiatric reports received from 2008 to 2013 for varenicline, 462 (81%) provided an event date, of which 131 (28%) occurred prior to 2008.

4 APPENDIX A

Table 3. MedDRA Preferred Terms (PTs) for Select Categories of Neuropsychiatric Events

Suicidality	Psychosis Mania	Aggression/Violent Behavior	Miscellaneous
Suicidal and self-injurious behavior NEC (HLGT)	Mania	Aggression	Abnormal behavior
Depression suicidal	Paranoia	Belligerence	Amnestic symptoms (HLT)
Gun shot wound	Catatonia	Anger	Confusional state
Intentional drug misuse	Hypomania	Hostility	Mood alterations with depressive symptoms (HLT)
Overdose	Schizotypical personality disorder	Physical assault	Depression
	Schizophrenia and other psychotic disorders (HLGT)	Sexual abuse	Major depression
	Delusion symptoms (HLT)	Homicide	Disorientation
	Perception disturbances (HLT)	Imprisonment	Emotional disorder
	Bipolar disorders (HLT)	Homicidal ideation	Emotional distress
	Schizoid personality disorder		Feeling abnormal
	Paranoid personality disorder		Mood altered

Table 3. MedDRA Preferred Terms (PTs) for Select Categories of Neuropsychiatric Events			
Suicidality	**Psychosis Mania**	**Aggression/Violent Behavior**	**Miscellaneous**
			Mood swings
			Personality change
			Thinking abnormal
			Anxiety disorders with symptoms (HLGT)
			Trichotillomania
			Sleep disorder
			Tic disorders (HLT)

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/s/

SARA L CAMILLI
05/16/2014

SCOTT E PROESTEL
05/16/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021928/S-036

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

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

Hi Lilya,

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

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

Thanks,
Ayanna

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

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/s/

AYANNA S AUGUSTUS
09/17/2014

From:	Augustus, Ayanna
To:	Donohew, Lilya (Lilya.Donohew@pfizer.com)
Subject:	Chantix/Labeling/S-036
Date:	Tuesday, September 09, 2014 10:27:40 AM
Attachments:	TRACKED - Chantix - PI 9 8 14.doc
Importance:	High

Hi Lilya,

Attached is the draft Chantix PI with the revisions discussed and agreed upon during Monday's tcon. Please note that we revised the following statement which was not discussed during the meeting:

[redacted] (b) (4) data are available from post-marketing smoking cessation studies in two patient groups: 1) patients with major depressive disorder [redacted] (b) (4), and 2) in patients with stable schizophrenia or schizoaffective disorder *[see Adverse Reactions (6.1)]*.

[redacted] (b) (4) in this statement because only approximately 100 patients with schizophrenia and 250 patients with depression have been treated with varenicline, and we consider this a limited amount of data. This revision is reflected in the attached label.

If Pfizer is in agreement with these revisions to the current PI, please submit the revised PI in tracked changes to S-036. Please do so by Tuesday, Sept 16th.

Best Regards,
Ayanna

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

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/s/

AYANNA S AUGUSTUS
09/09/2014

Jani, Parinda

From: Jani, Parinda
Sent: Friday, August 15, 2014 4:42 PM
To: Donohew, Lilya (Lilya.Donohew@pfizer.com)
Cc: Augustus, Ayanna
Subject: Chantix label
Attachments: Chanitx S036 PI tracked changes.doc; side by side comparison_5 1_neuropsych warning _clean.doc

Dear Lilya:

Attached is the proposed revisions to the label you had submitted for Chantix, NDA 21928/S-036.

The PI with tracked changes shows that [redacted] (b) (4), and adds information about the meta-analyses and observational studies in section 5.1 following the text describing the signal that is currently in the approved labeling.

The "side by side" comparison, shows what Pfizer originally proposed next to what the FDA proposal contains. There is also some rationale provided for revisions that have been made.

Regards,

Parinda Jani
Chief, Project Management Staff
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Tel # (301) 796-1232

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/s/

PARINDA JANI
08/15/2014

From:	Sullivan, Matthew
To:	"lilya.donohew@pfizer.com"
Cc:	Augustus, Ayanna
Subject:	NDA 21928 / S036
Date:	Thursday, May 22, 2014 6:29:57 PM

Dr Donohew –

I am covering for Ayanna Augustus, and have been asked to pass along a comment regarding NDA 21928, Supplement 36:

We have done a preliminary review of the data you submitted on April 8, 2014, in support of your proposed labeling changes regarding neuropsychiatric adverse events with Chantix (varenicline). We believe that there is information from the RCT meta-analyses and observational studies that could be added to labeling to provide balance to the information regarding the risk of neuropsychiatric adverse events. We will be working on drafting that labeling over the next two weeks. At this time (b) (4), as we anticipate that would be a topic of discussion at the advisory committee meeting planned for October 16, 2014.

Thanks, and please let me know if you have any questions.

Matt

Matthew W. Sullivan, M.S.
Supervisory Regulatory Health Project Manager
Division of Anesthesia, Analgesia,
and Addiction Products
Food and Drug Administration
Phone 301-796-1245
Fax 301-796-9723
matthew.sullivan@fda.hhs.gov

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/s/

MATTHEW W SULLIVAN
05/23/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 021928/S-036

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: 21928

SUPPLEMENT NUMBER: 036

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

DATE OF SUBMISSION: April 8, 2014

DATE OF RECEIPT: April 8, 2014

This supplemental application proposes changes to the Package Insert based on varenicline clinical trial and observational study data pertaining to neuropsychiatric symptoms adverse events.

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 **June 7, 2014**, in accordance with 21 CFR 314.101(a).

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). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

FDAAA TITLE VIII RESPONSIBILITIES

You are also responsible for complying with the applicable provisions of sections 402(i) and (j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this application. You may use Form FDA 3674, "Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank," [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at http://www.fda.gov/opacom/morechoices/fdaforms/default.html.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007," that describes the Agency's current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at:
http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm. Additional information regarding Title VIII of FDAAA is available at: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html. Additional information for registering your clinical trials is available at the Protocol Registration System website http://prsinfo.clinicaltrials.gov/.
When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to **NDA 021928/S-036** submitted on April 8, 20104, and that it contains the FDA Form 3674 that was to accompany that application.

If you have already submitted the certification for this application, please disregard the above.

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, call me, at (301) 796-3980.

Sincerely,

{See appended electronic signature page}

Ayanna Augustus, PhD, RAC
Sr. Regulatory Health Project Manager
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

AYANNA S AUGUSTUS
04/14/2014