CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

021928Orig1s039

Trade Name: CHANTIX

Generic or Proper Name: varenicline tartrate

Sponsor: Pfizer, Inc.

Approval Date: 08/12/2016

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-039

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**x**
Other Action Letters	
Labeling	**x**
REMS	**x**
Summary Review	**x**
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	**x**
Medical Review(s)	**x**
Chemistry Review(s)	
Environmental Assessment	
Pharmacology Review(s)	**x**
Statistical Review(s)	**x**
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	
Other Reviews	**x**
Risk Assessment and Risk Mitigation Review(s)	**x**
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	**x**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021928/S-039

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021928/S-039, S-041

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 13, 2015, and July 21, 2016, and your amendments, 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 also refer to our Safety Labeling Change notification letter dated July 15, 2016, 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 (varenicline). This information pertains to the risk of somnambulism.

These Prior Approval supplemental new drug applications propose the following revisions to the package insert:

S-039: Changes to the **DOSAGE AND ADMINISTRATION**, and **CLINICAL STUDIES** sections of the Package Insert, and modification to the approved risk evaluation and mitigation strategy (REMS) for Chantix, comprising of revisions to the **MEDICATION GUIDE**, to support the reduce-to-quit paradigm.

S-041: Consistent with our July 15, 2016, Safety Labeling Change notification letter, changes to the **WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS**, **PATIENT COUNSELING INFORMATION** sections of the labeling. S-041 also includes additional modification to the approved REMS, comprising further revisions to the **MEDICATION GUIDE** regarding the new safety information pertaining to risk of somnambulism.

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.

WAIVER OF HIGHLIGHTS SECTION

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information.

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 include 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 October 15, 2014. 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 add new language describing a reduce-to-quit regimen and to provide information about the risk of somnambulism so as to furnish adequate information for the safe and effective use of the drug.

Your proposed modified REMS, submitted on October 13, 2015, and appended to this letter, is approved.

The modified REMS consist 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.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any of goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A). This assessment should include:

a) An evaluation of how the benefit-risk profile will or will not change with the new indication;
b) A determination of the implications of a change in the benefit-risk profile for the current REMS;
c) *If the new, proposed indication for use introduces unexpected risks*: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.
d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: A statement about whether the REMS was meeting its goals at the time of the last assessment and if any modifications of the REMS have been proposed since that assessment.
e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.
f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rational to support the modification, including*: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing a REMS modification*, provide a rationale for why the REMS does not need to be modified.

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)

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.

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/S-000/
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 021928/S-000/
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 021928/S-000/
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES SUBMITTED IN SUPPLEMENT XXX

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 021928/S-000/
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISION FOR NDA 021928

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

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

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:

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

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, by fax to 301-847-8444, or electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

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}

Sharon Hertz, MD
Director
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/

SHARON H HERTZ
08/12/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021928/S-039

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, for oral use
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----------

Dosage and Administration, Usual Dosage for Adults (2.1)	8/2016
Warnings and Precautions, Somnambulism (5.6)	8/2016

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

----------DOSAGE AND ADMINISTRATION----------
- Begin CHANTIX dosing one week before the date set by the patient to stop smoking. Alternatively, the patient can begin CHANTIX dosing and then quit smoking between days 8 and 35 of treatment. (2.1)
- Starting week: 0.5 mg once daily on days 1-3 and 0 5 mg twice daily on days 4-7. (2.1)
- Continuing Weeks: 1 mg twice daily for a total of 12 weeks. (2.1)
- An additional 12 weeks of treatment is recommended for successful quitters to increase likelihood of long-term abstinence. (2.1)
- Consider a gradual approach to quitting smoking with CHANTIX for patients who are sure that they are not able or willing to quit abruptly. Patients should begin CHANTIX dosing and reduce smoking by 50% from baseline within the first four weeks, by an additional 50% in the next four weeks, and continue reducing with the goal of reaching complete abstinence by 12 weeks. Continue treatment for an additional 12 weeks, for a total of 24 weeks. (2.1)
- Severe Renal Impairment (estimated creatinine clearance less than 30 mL/min): Begin with 0.5 mg once daily and titrate to 0.5 mg twice daily. For patients with end-stage renal disease undergoing hemodialysis, a maximum of 0.5 mg daily may be given if tolerated. (2.2)
- Consider dose reduction for patients who cannot tolerate adverse effects. (2.1)
- Another attempt at treatment is recommended for those who fail to stop smoking or relapse when factors contributing to the failed attempt have been addressed. (2.1)
- Provide patients with appropriate educational materials and counseling to support the quit attempt. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------
Tablets: 0.5 mg and 1 mg (3)

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

----------WARNINGS AND PRECAUTIONS----------
- Seizures: New or worsening seizures have been observed in patients taking CHANTIX. CHANTIX should be used cautiously in patients with a history of seizures or other factors that can lower the seizure threshold. (5.2)
- Interaction with Alcohol: Increased effects of alcohol have been reported. Instruct patients to reduce the amount of alcohol they consume until they know whether CHANTIX affects them. (5.3)
- Accidental Injury: Accidental injuries (e.g., traffic accidents) have been reported. Instruct patients to use caution driving or operating machinery until they know how CHANTIX may affect them. (5.4)
- Cardiovascular Events: A meta-analysis of 15 clinical trials, including a trial in patients with stable cardiovascular (CV) disease, demonstrated that while cardiovascular events were infrequent overall, some were reported more frequently in patients treated with CHANTIX. These events occurred primarily in patients with known cardiovascular disease. In both the clinical trial and meta-analysis, all-cause and cardiovascular mortality was lower in patients treated with CHANTIX. Instruct patients to notify their healthcare providers of new or worsening cardiovascular symptoms and to seek immediate medical attention if they experience signs and symptoms of myocardial infarction (MI) or stroke. (5.5 and 6.1)
- Somnambulism: Cases of somnambulism have been reported in patients taking CHANTIX. Some cases described harmful behavior to self, others, or property. Instruct patients to discontinue CHANTIX and notify their healthcare provider if they experience somnambulism. (5.6 and 6.2)
- Angioedema and Hypersensitivity Reactions: Such reactions, including angioedema, infrequently life-threatening, have been reported. Instruct patients to discontinue CHANTIX and immediately seek medical care if symptoms occur. (5.7 and 6.2)
- Serious Skin Reactions: Rare, potentially life-threatening skin reactions have been reported. Instruct patients to discontinue CHANTIX and contact a healthcare provider immediately at first appearance of skin rash with mucosal lesions. (5.8 and 6.2)
- Nausea: Nausea is the most common adverse reaction (up to 30% incidence rate). Dose reduction may be helpful. (5.9)

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

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

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

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 08/2016

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), 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 orally after eating and with a full glass of water.

The recommended dose of CHANTIX is 1 mg twice daily following a 1-week titration as follows:

Days 1 – 3:	0.5 mg once daily
Days 4 – 7:	0.5 mg twice daily
Day 8 – end of treatment:	1 mg twice daily

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

For patients who are sure that they are not able or willing to quit abruptly, consider a gradual approach to quitting smoking with CHANTIX. Patients should begin CHANTIX dosing and reduce smoking by 50% from baseline within the first four weeks, by an additional 50% in the next four weeks, and continue reducing with the goal of reaching complete abstinence by 12 weeks. Continue CHANTIX treatment for an additional 12 weeks, for a total of 24 weeks of treatment. Encourage patients to attempt quitting sooner if they feel ready *[see Clinical Studies (14.5)]*.

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

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

2.2 Dosage in Special Populations

Patients with Impaired Renal Function

No dosage adjustment is necessary for patients with mild to moderate renal impairment. For patients with severe renal impairment (estimated creatinine clearance less than 30 mL per min), the recommended starting dose of CHANTIX is 0.5 mg once daily. The dose may then be titrated as needed to a maximum dose of 0.5 mg twice daily. For patients with end-stage renal disease undergoing hemodialysis, a maximum dose of 0.5 mg once daily may be administered if tolerated *[see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)]*.

Elderly and Patients with Impaired Hepatic Function

No dosage adjustment is necessary for patients with hepatic impairment. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function *[see Use in Specific Populations (8.5)]*.

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Neuropsychiatric Symptoms and Suicidality

Serious neuropsychiatric symptoms have been reported in patients being treated with CHANTIX *[see Boxed Warning, 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 postmarketing 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), Clinical Studies (14.8)]*.

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 Warnings and Precautions (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 Adverse Reactions (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 healthcare provider of new or worsening symptoms of cardiovascular disease. The risks of CHANTIX should be weighed against the benefits of its use in smokers with cardiovascular disease. Smoking is an independent and major risk factor for cardiovascular disease. CHANTIX has been demonstrated to increase the likelihood of abstinence from smoking for as long as one year compared to treatment with placebo.

5.6 Somnambulism

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

5.7 Angioedema and Hypersensitivity Reactions

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

5.8 Serious Skin Reactions

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

5.9 Nausea

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

6 ADVERSE REACTIONS

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

- Neuropsychiatric symptoms and suicidality *[see Boxed Warning, Warnings and Precautions (5.1)]*
- Seizures *[see Warnings and Precautions (5.2)]*
- Interaction with alcohol *[see Warnings and Precautions (5.3)]*
- Accidental injury *[see Warnings and Precautions (5.4)]*
- Cardiovascular events *[see Warnings and Precautions (5.5)]*
- Somnambulism *[see Warnings and Precautions (5.6)]*
- Angioedema and hypersensitivity reactions *[see Warnings and Precautions (5.7)]*
- Serious skin reactions *[see Warnings and Precautions (5.8)]*

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

The treatment discontinuation rate due to adverse events in patients dosed with 1 mg twice daily was 12% for CHANTIX, compared to 10% for placebo in studies of three months' treatment. In this group, the discontinuation rates that are higher than placebo for the most common adverse events in CHANTIX-treated patients were as follows: nausea (3% vs. 0.5% for placebo), insomnia (1.2% vs. 1.1% for placebo), and abnormal dreams (0 3% vs. 0.2% for placebo).

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

6.1 Clinical Trials Experience

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

During the premarketing development of CHANTIX, over 4500 subjects were exposed to CHANTIX, with over 450 treated for at least 24 weeks and approximately 100 for a year. Most study participants were treated for 12 weeks or less.

The most common adverse event associated with CHANTIX treatment is nausea, occurring in 30% of patients treated at the recommended dose, compared with 10% in patients taking a comparable placebo regimen *[see Warnings and Precautions (5.9)]*.

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

MedDRA High Level Group Terms (HLGT) reported in ≥ 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 Nutrition Disorders			
Increased appetite	4	3	2
Decreased appetite/ Anorexia	1	2	1

* Includes PTs Abdominal (pain, pain upper, pain lower, discomfort, tenderness, distension) and Stomach discomfort
** Includes PTs Insomnia/Initial insomnia/Middle insomnia/Early morning awakening

The overall pattern and frequency of adverse events during the longer-term premarketing trials was similar to those described in Table 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 premarketing clinical trials and updated based on pooled data from 18 placebo-controlled pre- and post-marketing studies, including approximately 5,000 patients treated with varenicline. Adverse events were categorized using MedDRA, Version 16.0. The listing does not include those events already listed in the previous tables or elsewhere in labeling, those events for which a drug cause was remote, those events which were so general as to be uninformative, and those events reported only once which did not have a substantial probability of being acutely life-threatening.

Blood and Lymphatic System Disorders. *Infrequent* anemia, lymphadenopathy. *Rare* leukocytosis, splenomegaly, thrombocytopenia.
Cardiac Disorders. *Infrequent* angina pectoris, myocardial infarction, palpitations, tachycardia. *Rare* acute coronary syndrome, arrhythmia, atrial fibrillation, bradycardia, cardiac flutter, cor pulmonale, coronary artery disease, ventricular extrasystoles.

Ear and Labyrinth Disorders. *Infrequent* tinnitus, vertigo. *Rare* deafness, Meniere's disease.
Endocrine Disorders. *Infrequent* thyroid gland disorders.
Eye Disorders. *Infrequent* conjunctivitis, eye irritation, eye pain, vision blurred, visual impairment. *Rare* blindness transient, cataract subcapsular, dry eye, night blindness, ocular vascular disorder, photophobia, vitreous floaters.
Gastrointestinal Disorders. *Frequent* diarrhea, toothache. *Infrequent* dysphagia, eructation, gastritis, gastrointestinal hemorrhage, mouth ulceration. *Rare* enterocolitis, esophagitis, gastric ulcer, intestinal obstruction, pancreatitis acute.
General Disorders and Administration Site Conditions. *Frequent* chest pain. *Infrequent* chest discomfort, chills, edema, influenza-like illness, pyrexia.
Hepatobiliary Disorders. *Rare* gall bladder disorder.
Investigations. *Frequent* liver function test abnormal, weight increased. *Infrequent* electrocardiogram abnormal. *Rare* muscle enzyme increased, urine analysis abnormal.
Metabolism and Nutrition Disorders. *Infrequent* diabetes mellitus, hypoglycemia. *Rare* hyperlipidemia, hypokalemia.
Musculoskeletal and Connective Tissue Disorders. *Frequent*: arthralgia, back pain, myalgia. *Infrequent* arthritis, muscle cramp, musculoskeletal pain. *Rare* myositis, osteoporosis.
Nervous System Disorders. *Frequent* disturbance in attention, dizziness. *Infrequent* amnesia, convulsion, migraine, parosmia, syncope, tremor. *Rare* balance disorder, cerebrovascular accident, dysarthria, mental impairment, multiple sclerosis, VIIth nerve paralysis, nystagmus, psychomotor hyperactivity, psychomotor skills impaired, restless legs syndrome, sensory disturbance, transient ischemic attack, visual field defect.
Psychiatric Disorders. *Infrequent* dissociation, libido decreased, mood swings, thinking abnormal. *Rare* bradyphrenia, disorientation, euphoric mood.
Renal and Urinary Disorders. *Infrequent* nocturia, pollakiuria, urine abnormality. *Rare* nephrolithiasis, polyuria, renal failure acute, urethral syndrome, urinary retention.
Reproductive System and Breast Disorders. *Frequent* menstrual disorder. *Infrequent* erectile dysfunction. *Rare* sexual dysfunction.
Respiratory, Thoracic and Mediastinal Disorders. *Frequent* respiratory disorders. *Infrequent* asthma, epistaxis, rhinitis allergic, upper respiratory tract inflammation. *Rare* pleurisy, pulmonary embolism.
Skin and Subcutaneous Tissue Disorders. *Infrequent* acne, dry skin, eczema, erythema, hyperhidrosis, urticaria. *Rare* photosensitivity reaction, psoriasis.
Vascular Disorders. *Infrequent* hot flush. *Rare* thrombosis.

CHANTIX has also been studied in postmarketing trials including (1) a trial conducted in patients with chronic obstructive pulmonary disease (COPD), (2) a trial conducted in generally healthy patients (similar to those in the premarketing studies) in which they were allowed to select a quit date between days 8 and 35 of treatment ("alternative quit date instruction trial"), (3) a trial conducted in patients who did not succeed in stopping smoking during prior CHANTIX therapy, or who relapsed after treatment ("re-treatment trial"), (4) a trial conducted in patients with stable cardiovascular disease, (5) a trial conducted in patients with stable schizophrenia or schizoaffective disorder (6) a trial conducted in patients with major depressive disorder and (7) a trial in patients who were not able or willing to quit abruptly and who were instructed to quit gradually ("gradual approach to quitting smoking trial").

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

In the trial of patients with stable cardiovascular disease, more types and a greater number of cardiovascular events were reported compared to premarketing studies. Treatment-emergent (on-treatment or 30 days after treatment) cardiovascular events reported with a frequency ≥ 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.

In the trial of patients with major depressive disorder, the most common adverse events (≥ 10%) in subjects taking varenicline were nausea (27% vs. 10% on placebo), headache (17 vs 11%), abnormal dreams (11% vs 8%), insomnia (11% vs 5%) and irritability (11% vs. 8%). Additionally, the following psychiatric AEs were reported in ≥ 2% of patients in either treatment group (varenicline or placebo, respectively): anxiety (7% vs. 9%), agitation (7% vs. 4%), depressed mood disorders and disturbances (11% vs. 9%), tension (4% vs. 3%), hostility (2% vs. 0.4%) and restlessness (2% vs. 2%). Patients treated with varenicline were more likely than patients treated with placebo to report one of various events related to hostility and aggression (3% vs 1%). Psychiatric scales showed no differences between the varenicline and placebo groups and no overall worsening of depression during the study in either treatment group. The percentage of subjects with suicidal ideation and/or behavior was similar between the varenicline and placebo groups during treatment (6% and 8%, respectively) and the non-treatment follow-up (6% and 6%, respectively). There was one event of intentional self-injury/possible suicide attempt during treatment (Day 73) in a subject in the placebo group. Suicide could not be ruled out in one subject who died by an overdose of illicit drugs 76 days after last dose of study drug in the varenicline group.

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

There have been postmarketing reports of patients experiencing increased intoxicating effects of alcohol while taking CHANTIX. Some reported

neuropsychiatric events, including unusual and sometimes aggressive behavior *[see Warnings and Precautions (5.1) and (5.3)]*.

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

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

There have been reports of myocardial infarction (MI) and cerebrovascular accident (CVA) including ischemic and hemorrhagic events in patients taking CHANTIX. In the majority of the reported cases, patients had pre-existing cardiovascular disease and/or other risk factors. Although smoking is a risk factor for MI and CVA, based on temporal relationship between medication use and events, a contributory role of varenicline cannot be ruled out *[see Warnings and Precautions (5.5)]*.

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

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

7 DRUG INTERACTIONS

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

7.1 Use with Other Drugs for Smoking Cessation

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

Bupropion

Varenicline (1 mg twice daily) did not alter the steady-state pharmacokinetics of bupropion (150 mg twice daily) in 46 smokers. The safety of the combination of bupropion and varenicline has not been established.

Nicotine replacement therapy (NRT)

Although co-administration of varenicline (1 mg twice daily) and transdermal nicotine (21 mg/day) for up to 12 days did not affect nicotine pharmacokinetics, the incidence of nausea, headache, vomiting, dizziness, dyspepsia, and fatigue was greater for the combination than for NRT alone. In this study, eight of twenty-two (36%) patients treated with the combination of varenicline and NRT prematurely discontinued treatment due to adverse events, compared to 1 of 17 (6%) of patients treated with NRT and placebo.

7.2 Effect of Smoking Cessation on Other Drugs

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

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

Clinical Considerations

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

Data

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

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

8.2 Lactation

Risk Summary

There are no data on the presence of varenicline in human milk, the effects on the breastfed infant, or the effects on milk production. In animal studies varenicline was present in milk of lactating rats *[see Data]*. However, due to species-specific differences in lactation physiology, animal data may not reliably predict drug levels in human milk. The lack of clinical data during lactation precludes a clear determination of the risk of CHANTIX to an infant during lactation; however the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for CHANTIX and any potential adverse effects on the breastfed child from CHANTIX or from the underlying maternal condition.

Clinical Considerations

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

Data

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

8.4 Pediatric Use

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

8.5 Geriatric Use

A combined single- and multiple-dose pharmacokinetic study demonstrated that the pharmacokinetics of 1 mg varenicline given once daily or twice daily to 16 healthy elderly male and female smokers (aged 65-75 years) for 7 consecutive days was similar to that of younger subjects. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Varenicline is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function [*see Dosage and Administration (2.2)*].

No dosage adjustment is recommended for elderly patients.

8.6 Renal Impairment

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

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Varenicline is not a controlled substance.

9.3 Dependence

Humans

Fewer than 1 out of 1,000 patients reported euphoria in clinical trials with CHANTIX. At higher doses (greater than 2 mg), CHANTIX produced more frequent reports of gastrointestinal disturbances such as nausea and vomiting. There is no evidence of dose-escalation to maintain therapeutic effects in clinical studies, which suggests that tolerance does not develop. Abrupt discontinuation of CHANTIX was associated with an increase in irritability and sleep disturbances in up to 3% of patients. This suggests that, in some patients, varenicline may produce mild physical dependence which is not associated with addiction.

In a human laboratory abuse liability study, a single oral dose of 1 mg varenicline did not produce any significant positive or negative subjective responses in smokers. In non-smokers, 1 mg varenicline produced an increase in some positive subjective effects, but this was accompanied by an increase in negative adverse effects, especially nausea. A single oral dose of 3 mg varenicline uniformly produced unpleasant subjective responses in both smokers and non-smokers.

Animals

Studies in rodents have shown that varenicline produces behavioral responses similar to those produced by nicotine. In rats trained to discriminate nicotine from saline, varenicline produced full generalization to the nicotine cue. In self-administration studies, the degree to which varenicline substitutes for nicotine is dependent upon the requirement of the task. Rats trained to self-administer nicotine under easy conditions continued to self-administer varenicline to a degree comparable to that of nicotine; however in a more demanding task, rats self-administered varenicline to a lesser extent than nicotine. Varenicline pretreatment also reduced nicotine self-administration.

10 OVERDOSAGE

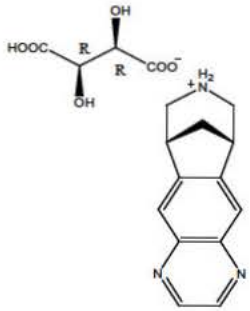
In case of overdose, standard supportive measures should be instituted as required.

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

11 DESCRIPTION

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

Varenicline, as the tartrate salt, is a powder which is a white to off-white to slightly yellow solid with the following chemical name: 7,8,9,10-tetrahydro-6,10-methano-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, >3,500-fold α7, >20,000-fold α1βγδ), or to non-nicotinic receptors and transporters (>2,000-fold). Varenicline also binds with moderate affinity (Ki = 350 nM) to the 5-HT3 receptor.

12.3 Pharmacokinetics

Absorption

Maximum plasma concentrations of varenicline occur typically within 3-4 hours after oral administration. Following administration of multiple oral doses of varenicline, steady-state conditions were reached within 4 days. Over the recommended dosing range, varenicline exhibits linear pharmacokinetics after single or repeated doses.

In a mass balance study, absorption of varenicline was virtually complete after oral administration and systemic availability was ~90%.

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

Distribution

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

Elimination

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

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

Excretion

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

Specific Populations

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

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

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

Renal Impairment
Varenicline pharmacokinetics were unchanged in subjects with mild renal impairment (estimated creatinine clearance >50 mL/min and ≤80 mL/min). In subjects with moderate renal impairment (estimated creatinine clearance ≥30 mL/min and ≤50 mL/min), varenicline exposure increased 1.5-fold compared with subjects with normal renal function (estimated creatinine clearance >80 mL/min). In subjects with severe renal impairment (estimated creatinine clearance <30 mL/min), varenicline exposure was increased 2.1-fold. In subjects with end-stage-renal disease (ESRD) undergoing a three-hour session of hemodialysis for three days a week, varenicline exposure was increased 2.7-fold following 0.5 mg once daily administration for 12 days. The plasma 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), Use in Specific Populations (8.6)]*. Additionally, in subjects with ESRD, varenicline was efficiently removed by hemodialysis *[see Overdosage (10)]*.

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

Drug-Drug Interactions

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

In vitro studies demonstrated that varenicline does not inhibit human renal transport proteins at therapeutic concentrations. Therefore, drugs that are cleared by renal secretion (e.g., metformin *[see below]*) are unlikely to be affected by varenicline.

In vitro studies demonstrated the active renal secretion of varenicline is mediated by the human organic cation transporter OCT2. Co-administration with inhibitors of OCT2 (e.g., 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.

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

Metformin
When co-administered to 30 smokers, varenicline (1 mg twice daily) did not alter the steady-state pharmacokinetics of metformin (500 mg twice daily), which is a substrate of OCT2. Metformin had no effect on varenicline steady-state pharmacokinetics.

Cimetidine
Co-administration of an OCT2 inhibitor, cimetidine (300 mg four times daily), with varenicline (2 mg single dose) to 12 smokers increased the systemic exposure of varenicline by 29% (90% CI: 21.5%, 36.9%) due to a reduction in varenicline renal clearance.

Digoxin
Varenicline (1 mg twice daily) did not alter the steady-state pharmacokinetics of digoxin administered as a 0.25 mg daily dose in 18 smokers.

Warfarin
Varenicline (1 mg twice daily) did not alter the pharmacokinetics of a single 25 mg dose of (R, S)-warfarin in 24 smokers. Prothrombin time (INR) was not affected by varenicline. Smoking cessation itself may result in changes to warfarin pharmacokinetics *[see Drug Interactions (7.2)]*.

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

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Lifetime carcinogenicity studies were performed in CD-1 mice and Sprague-Dawley rats. There was no evidence of a carcinogenic effect in mice administered varenicline by oral gavage for 2 years at doses up to 20 mg/kg/day (47 times the maximum recommended human daily (MRHD) exposure based on AUC). Rats were administered varenicline (1, 5, and 15 mg/kg/day) by oral gavage for 2 years. In male rats (n = 65 per sex per dose group), incidences of hibernoma (tumor of the brown fat) were increased at the mid dose (1 tumor, 5 mg/kg/day, 23 times the MRHD exposure based on AUC) and maximum dose (2 tumors, 15 mg/kg/day, 67 times the MRHD exposure based on AUC). The clinical relevance of this finding to humans has not been established. There was no evidence of carcinogenicity in female rats.

Mutagenesis

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

Impairment of Fertility

There was no evidence of impairment of fertility in either male or female Sprague-Dawley rats administered varenicline succinate up to 15 mg/kg/day (67 and 36 times, respectively, the MRHD exposure based on AUC at 1 mg twice daily). Maternal toxicity, characterized by a decrease in body weight gain, was observed at 15 mg/kg/day. However, a decrease in fertility was noted in the offspring of pregnant rats who were administered varenicline succinate at an oral dose of 15 mg/kg/day. This decrease in fertility in the offspring of treated female rats was not evident at an oral dose of 3 mg/kg/day (9 times the MRHD exposure based on AUC at 1 mg twice daily).

14 CLINICAL STUDIES

The efficacy of CHANTIX in smoking cessation was demonstrated in six clinical trials in which a total of 3659 chronic cigarette smokers (≥10 cigarettes per day) were treated with CHANTIX. In all clinical studies, abstinence from smoking was determined by patient self-report and verified by measurement of exhaled carbon monoxide (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.

Six additional studies were conducted in patients with cardiovascular disease, in patients with chronic obstructive pulmonary disease *[see Clinical Studies (14.7)]*, in patients instructed to select their quit date within days 8 and 35 of treatment *[see Clinical Studies (14.4)]*, patients with major depressive disorder *[see Clinical Studies (14.8)]*, patients who had made a previous attempt to quit smoking with CHANTIX, and either did not succeed in quitting or relapsed after treatment *[see Clinical Studies (14.6)]*, and in patients who were not able or willing to quit abruptly and were instructed to quit gradually *[see Clinical studies (14.5)]*.

In all studies, patients were provided with an educational booklet on smoking cessation and received up to 10 minutes of smoking cessation counseling at each weekly treatment visit according to Agency for Healthcare Research and Quality guidelines.

14.1 Initiation of Abstinence

Study 1

This was a six-week dose-ranging study comparing CHANTIX to placebo. This study provided initial evidence that CHANTIX at a total dose of 1 mg per day or 2 mg per day was effective as an aid to smoking cessation.

Study 2

This study of 627 patients compared CHANTIX 1 mg per day and 2 mg per day with placebo. Patients were treated for 12 weeks (including one-week titration) and then were followed for 40 weeks post-treatment. CHANTIX was given in two divided doses daily. Each dose of CHANTIX was given in two different regimens, with and without initial dose-titration, to explore the effect of different dosing regimens on tolerability. For the titrated groups, dosage was titrated up over the course of one week, with full dosage achieved starting with the second week of dosing. The titrated and nontitrated groups were pooled for efficacy analysis.

Forty-five percent of patients receiving CHANTIX 1 mg per day (0.5 mg twice daily) and 51% of patients receiving 2 mg per day (1 mg twice daily) had CO-confirmed continuous abstinence during weeks 9 through 12 compared to 12% of patients in the placebo group (Figure 1). In addition, 31% of the 1 mg per day group and 31% of the 2 mg per day group were continuously abstinent from one week after TQD through the end of treatment as compared to 8% of the placebo group.

Study 3

This flexible-dosing study of 312 patients examined the effect of a patient-directed dosing strategy of CHANTIX or placebo. After an initial one-week titration to a dose of 0 5 mg twice daily, patients could adjust their dosage as often as they wished between 0.5 mg once daily to 1 mg twice daily per day. Sixty-nine percent of patients titrated to the maximum allowable dose at any time during the study. For 44% of patients, the modal dose selected was 1 mg twice daily; for slightly over half of the study participants, the modal dose selected was 1 mg/day or less.

Of the patients treated with CHANTIX, 40% had CO-confirmed continuous abstinence during weeks 9 through 12 compared to 12% in the placebo group. In addition, 29% of the CHANTIX group were continuously abstinent from one week after TQD through the end of treatment as compared to 9% of the placebo group.

Study 4 and Study 5

These identical double-blind studies compared CHANTIX 2 mg per day, bupropion sustained-release (SR) 150 mg twice daily, and placebo. Patients were treated for 12 weeks and then were followed for 40 weeks post-treatment. The CHANTIX dosage of 1 mg twice daily was achieved using a titration of 0.5 mg once daily for the initial 3 days followed by 0.5 mg twice daily for the next 4 days. The bupropion SR dosage of 150 mg twice daily was achieved using a 3-day titration of 150 mg once daily. Study 4 enrolled 1022 patients and Study 5 enrolled 1023 patients. Patients inappropriate for bupropion treatment or patients who had previously used bupropion were excluded.

In Study 4, patients treated with CHANTIX had a superior rate of CO-confirmed abstinence during weeks 9 through 12 (44%) compared to patients treated with bupropion SR (30%) or placebo (17%). The bupropion SR quit rate was also superior to placebo. In addition, 29% of the CHANTIX group were continuously abstinent from one week after TQD through the end of treatment as compared to 12% of the placebo group and 23% of the bupropion SR group.

Similarly in Study 5, patients treated with CHANTIX had a superior rate of CO-confirmed abstinence during weeks 9 through 12 (44%) compared to patients treated with bupropion SR (30%) or placebo (18%). The bupropion SR quit rate was also superior to placebo. In addition, 29% of the CHANTIX group were continuously abstinent from one week after TQD through the end of treatment as compared to 11% of the placebo group and 21% of the bupropion SR group.

Figure 1: Continuous Abstinence, Weeks 9 through 12

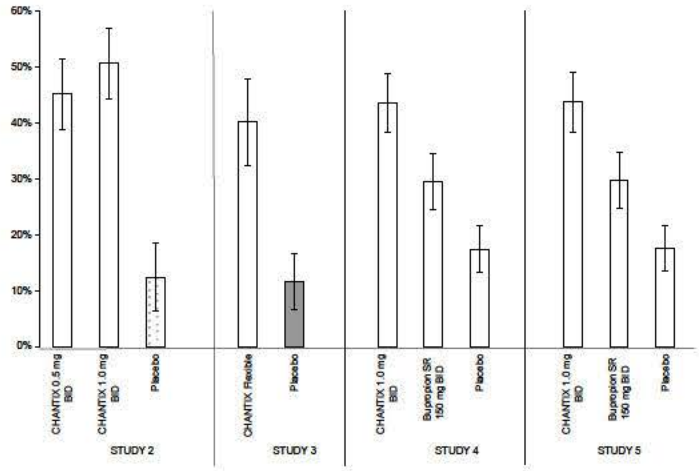


Table 6: Continuous Abstinence, Weeks 9 through 12 (95% confidence interval)

	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

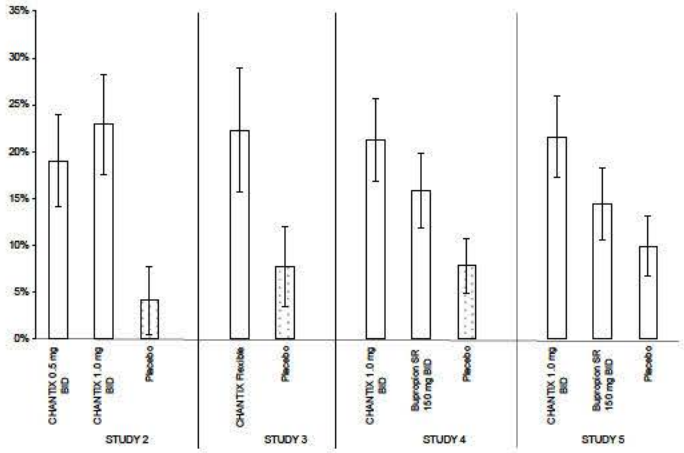


Table 7: Continuous Abstinence, Weeks 9 through 52 (95% confidence interval) Across Different Studies

	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

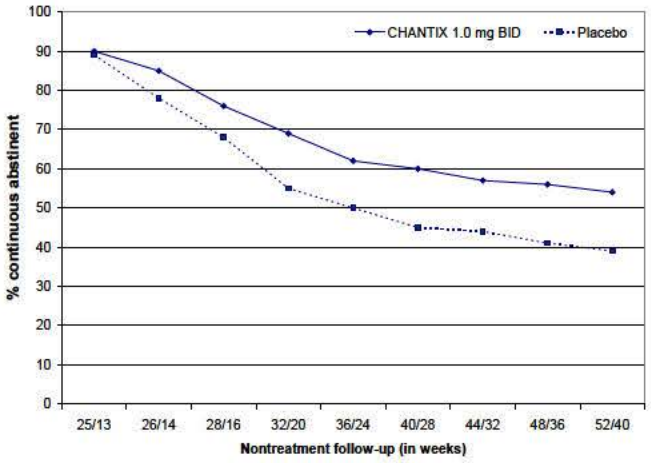
Study 6

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 Alternative Instructions for Setting a Quit Date

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

14.5 Gradual Approach to Quitting Smoking

CHANTIX was evaluated in a 52-week double-blind placebo-controlled study of 1,510 subjects who were not able or willing to quit smoking within four weeks, but were willing to gradually reduce their smoking over a 12 week period before quitting. Subjects were randomized to either CHANTIX 1 mg twice daily (n=760) or placebo (n=750) for 24 weeks and followed up post-treatment through week 52. Subjects were instructed to reduce the number of cigarettes smoked by at least 50 percent by the end of the first four weeks of treatment, followed by a further 50 percent reduction from week four to week eight of treatment, with the goal of reaching complete abstinence by 12 weeks. After the initial 12-week reduction phase, subjects continued treatment for another 12 weeks. Subjects treated with CHANTIX had a significantly higher Continuous Abstinence Rate compared with placebo at weeks 15 through 24 (32% vs. 7%) and weeks 15 through 52 (24% vs. 6%).

14.6 Re-Treatment Study

CHANTIX was evaluated in a double-blind, placebo-controlled trial of patients who had made a previous attempt to quit smoking with CHANTIX, and either did not succeed in quitting or relapsed after treatment. Subjects were randomized 1:1 to CHANTIX 1 mg twice daily (n=249) or placebo (n=245) for 12 weeks of treatment and followed for 40 weeks post-treatment. Patients included in this study had taken CHANTIX for a smoking-cessation attempt in the past (for a total treatment duration of a minimum of two weeks), at least three months prior to study entry, and had been smoking for at least four weeks.

Patients treated with CHANTIX had a superior rate of CO-confirmed abstinence during weeks 9 through 12 (45%) compared to patients treated with placebo (12%) and from weeks 9 through 52 (20%) compared to subjects treated with placebo (3%).

Table 8: Continuous Abstinence (95% confidence interval), Re-Treatment Study

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

BID = twice daily

14.7 Subjects with Cardiovascular and Chronic Obstructive Pulmonary Disease

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

CHANTIX was evaluated in a randomized, double-blind, placebo-controlled study of subjects aged ≥ 35 years with mild-to-moderate COPD with post-bronchodilator FEV_1/FVC <70% and $FEV_1 \geq 50\%$ of predicted normal value. Subjects were randomized to CHANTIX 1 mg twice daily (n=223) or placebo (n=237) for a treatment of 12 weeks and then were followed for 40 weeks post-treatment. Subjects treated with CHANTIX had a superior rate of CO-confirmed abstinence during weeks 9 through 12 (41%) compared to subjects treated with placebo (9%) and from week 9 through 52 (19%) compared to subjects treated with placebo (6%).

Table 9: Continuous Abstinence (95% confidence interval), Studies in Patients with Cardiovascular Disease (CVD) and Chronic Obstructive Pulmonary Disease (COPD)

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

BID = twice daily

14.8 Subjects with Major Depressive Disorder

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

Table 10: Continuous Abstinence (95% confidence interval), Study in Patients with Major Depressive Disorder (MDD)

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

BID = twice daily

16 HOW SUPPLIED/STORAGE AND HANDLING

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

	Description	NDC
Packs	Starting 2 week card: 0.5 mg x 11 tablets and 1 mg x 14 tablets	NDC 0069-0471-01
	Continuing 2 week card: 1 mg x 28 tablets	NDC 0069-0469-11
	Starting 4-week card: 0.5 mg x 11 tablets and 1 mg x 42 tablets	NDC 0069-0471-03
	Continuing 4-week card: 1 mg x 56 tablets	NDC 0069-0469-03
	Starting Month Box: 0 5 mg x 11 tablets and 1 mg x 42 tablets	NDC 0069-0471-02; NDC 0069-0471-03
	Continuing Month Box: 1 mg x 56 tablets	NDC 0069-0469-12; NDC 0069-0469-03
Bottles	0.5 mg - bottle of 56	NDC 0069-0468-56
	1 mg - bottle of 56	NDC 0069-0469-56

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

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide)

Initiate Treatment and Continue to Attempt to Quit if Lapse

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

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

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

How to Take

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

Starting Week Dosage

Instruct patients on how to titrate CHANTIX, beginning at a dose of 0.5 mg/day. Explain that one 0 5 mg tablet should be taken daily for the first three days, and that for the next four days, one 0.5 mg tablet should be taken in the morning and one 0.5 mg tablet should be taken in the evening *[see Dosage and Administration (2.1)]*.

Continuing Weeks Dosage

Advise patients that, after the first seven days, the dose should be increased to one 1 mg tablet in the morning and one 1 mg tablet in the evening *[see Dosage and Administration (2.1)]*.

Dosage Adjustment for CHANTIX or Other Drugs

Inform patients that nausea and insomnia are side effects of CHANTIX and are usually transient; however, advise patients that if they are persistently troubled by these symptoms, they should notify the prescribing physician so that a dose reduction can be considered.

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

Counseling and Support

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

Neuropsychiatric 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)]*.

History of Psychiatric Illness

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

Nicotine Withdrawal

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

Seizures

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

Interaction with Alcohol

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

Driving or Operating Machinery

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

Cardiovascular Events

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

Somnambulism

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

Angioedema

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

Serious Skin Reactions

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

Vivid, Unusual, or Strange Dreams

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

Pregnancy and Lactation

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

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

LAB- 0327-20.5

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. If you breastfeed and take CHANTIX, monitor your baby for seizures as well as spitting up or vomiting more than normal.

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 3 ways that you can use CHANTIX to help you quit smoking. Talk to your doctor about the following 3 ways to use CHANTIX:
  - Choose a **quit date** when you will stop smoking. Start taking CHANTIX 1 week (7 days) before your **quit date**. Take CHANTIX for 12 weeks.

    OR
  - Start taking CHANTIX before you choose a **quit date.** Pick a date to quit smoking that is between days 8 and 35 of treatment. Take CHANTIX for 12 weeks.

    OR
  - If you are sure that you are not able or willing to quit smoking right away, start taking CHANTIX and reduce smoking during the first 12 weeks of treatment, as follows:

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

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

  Starting CHANTIX before your **quit date** gives CHANTIX time to build up in your body. You can keep smoking during this time. Take CHANTIX exactly as prescribed by your 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	o White tablet (0.5 mg) o Take 1 tablet each day
Day 4 to Day 7	o White tablet (0.5 mg) Take 1 in the morning and 1 in the evening
Day 8 to end of treatment	o Blue tablet (1 mg) o 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:
  - increased drunkenness (intoxication)
  - unusual or sometimes aggressive behavior
  - 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 doctor 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
- **Sleepwalking** can happen with CHANTIX, and can sometimes lead to behavior that is harmful to you or other people, or to property. Stop taking CHANTIX and tell your doctor if you start sleepwalking.
- **Allergic reactions** can happen with CHANTIX. Some of these allergic reactions can be life-threatening.
- **Serious skin reactions**, including rash, swelling, redness, and peeling of the skin. Some of these skin reactions can become life-threatening.

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

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

The most common side effects of CHANTIX include:

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

Tell your 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 the safe and effective use of CHANTIX

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

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

What are the ingredients in CHANTIX?

Active ingredient: varenicline tartrate

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

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: August 2016

LAB 0328-13.4

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021928/S-039

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/

SHARON H HERTZ
08/12/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021928/S-039

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Sharon Hertz, MD
Subject	Division Director Summary Review
NDA /Supplement #	21928/ S039
Applicant Name	Pfizer, Inc.
Date of Submission	October 13, 2015
PDUFA Goal Date	August 13, 2016
Proprietary Name / Established (USAN) Name	Chantix (varenicline tartrate) tablet, film coated
Dosage Forms / Strength	Oral tablets, 0.5 mg and 1 mg
Proposed Indication(s)	1. Aid to smoking cessation treatment
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Sarah Arnold, MD
Statistical Review	Katherine Meaker, MS, David Petullo, PhD
Pharmacology/Toxicology Review	Kevin Snyder, PhD, Newton Woo, PhD
CDTL Review	Celia Winchell, MD
OSE/DPV OSE/DMEPA OSE/DRISK	Martin Pollack, PharmD, Laurelle Cascio, PharmD, and Jane Gilbert, MD Millie Shah, PharmD, BCPS, Vicky Borders-Hemphill, PharmD Danny S. Gonzalez, PharmD, MS, Kimberly Lehrfeld, PharmD
DPMH	Leyla Sahin, MD, Tamara Johnson, MD, MS
OMP/OPDP	L. Shenee Toombs, PhD, Sharon Mills, BSN, RN, CCRP, Barbara Fuller, RN, MSN, CWOCN, LaShawn Griffiths, MSHS-PH, BSN, RN

OND=Office of New Drugs
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Errors Prevention
DSI=Division of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OPDP=Office of Prescription Drug Promotion
DCDP=Division of Consumer Drug Promotion
OMP=Office of Medical Policy Initiatives
DMPP=Division of Medical Policy Programs

Signatory Authority Review Template

1. Introduction

This application is an efficacy supplement submitted to add language to the dosage and administration in support of a "reduce to quit" (RTQ) regimen based on the results of a single new, randomized, placebo-controlled efficacy trial, Study A3051075, in which patients were instructed in quitting smoking via gradual reduction, rather than abruptly. Chantix is currently indicated as an aid to smoking cessation. Dr. Celia Winchell has written a detailed Cross Discipline Team Leader Review that captures a detailed assessment of the clinical and statistical reviews and provides a background about the concept of gradually reducing the number of cigarettes smoked over time.

2. Background

Varenicline is a high-affinity selective partial agonist of the α4β2 nicotinic receptor, previously designated CP526-555 and developed under IND 58,994 and was approved on (b) (4). The α4β2 nicotinic receptor has been shown to be responsible for the reinforcing properties of nicotine in animal models. Varenicline is thought help patients stop smoking by mitigating withdrawal symptoms and reducing the reinforcing effects of nicotine. Chantix was originally labeled with instructions for patients to initiate a 12-week course of Chantix one week before a prespecified quit date, titrate up to the 1 mg twice daily dose over the first week, and then attempt to quit. Data from a randomized withdrawal trial in successful quitters also supported a recommendation for a second course of 12 weeks to improve long-term abstinence. Data from a clinical trial supported the addition of a "flexible approach to setting a quit date" to the Dosing and Administration section in which patients begin taking Chantix without having set a particular quit date and choose one between Day 8 and Week 5. Both approaches demonstrated statistically significant effects of Chantix on both initial quit (measured over the last month of treatment) and sustained abstinence (continued to the end of a year of observation, 40 weeks post-treatment).

The current submission is intended to allow for patients to gradually reduce smoking over a period of three months of treatment, and then to continue Chantix for three additional months after quitting.

As discussed by Dr. Winchell, there has long been interest in developing RTQ approaches to smoking cessation, because it is thought that for smokers who are reluctant to quit, the prospect of RTQ is considered an attractive option.

3. CMC/Device

There were no new CMC data submitted in support of this application.

4. Nonclinical Pharmacology/Toxicology

There were no new nonclinical data submitted in support of this application.

5. Clinical Pharmacology/Biopharmaceutics

There were no new pharmacokinetic data submitted in support of this application.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

One clinical trial was submitted in support of this supplemental application. See the reviews by Drs. Winchell and Arnold and Ms. Meaker for full details. Study A3051075 was a Phase 4, multi-national, randomized, double-blind, placebo controlled study to evaluate the efficacy and safety of varenicline compared to placebo for smoking cessation through reduction. Most of the following information has been excerpted with little modification from Dr. Winchell's review.

The study enrolled adult smokers of at least 10 cigarettes/day (on average, over the past year and during the month prior to screening) who were not willing/able to quit smoking within the next month but who were willing to attempt to reduce their smoking to work toward a quit attempt within the next 3 months. Key exclusion criteria included pregnancy, nursing, unstable and more than mild-to-moderate severity psychiatric conditions, substance use disorders, relevant medical conditions such as severe COPD, recent significant cardiovascular or cerebrovascular disease, or recent cancer.

During the first 4 weeks of treatment subjects were to reduce the number of cigarettes smoked by at least 50% from baseline; by 8 weeks they would reduce by 50% again (75% from baseline); and at Week 12 the intent was to quit entirely. Treatment with study drug continued through Week 24.

Disallowed concomitant medications included other smoking cessation aids, as well as some other medications thought to affect or be affected by smoking cessation[1].

Patients were randomly assigned at a 1:1 ratio to treatment with varenicline or placebo. Dosing followed the labeled regimen: 1 week run-in titration (0.5 mg twice daily for 3 days; 1.0 mg twice daily for 4 days, then increase to 1 mg twice daily dosing in Week 2 through Week 24. The blinded dose could be lowered temporarily or permanently to 0.5 mg twice daily for tolerability. Patients were followed for 28 weeks after treatment (52 weeks total) to assess continued abstinence from smoking. Use of nicotine replacement therapy or other nicotine-containing products was prohibited during the study.

Subjects were instructed to reduce the number of cigarettes smoked by at least 50 percent by the end of the first four weeks of treatment, followed by a further 50 percent reduction from week four to week eight of treatment, with the goal of reaching complete abstinence by 12 weeks. After the initial 12-week reduction phase, subjects continued treatment for another 12 weeks.

All participants were to receive up to 10 minutes of smoking cessation counseling in accordance with Agency for Healthcare Research and Quality (AHRQ) guidelines2 or similar local guidelines, at each clinic visit and telephone contact starting with the Baseline visit.

The pre-specified primary endpoint was exhaled carbon monoxide (CO)-confirmed 10-week continuous abstinence (CA), with the 10 weeks being counted from Weeks 15-24, inclusive, using patient self-reports of cigarette and nicotine use 'since last visit' and CO measurements conducted in the clinic visit. Subjects were to be classified as responders if they were able to maintain complete abstinence from cigarette smoking and other nicotine use for the last 10 weeks of treatment with end-expiratory exhaled CO measurements ≤ 10 ppm.

A total of 1510 patients were randomized and 1493 received treatment. Patient demographics were reasonably balanced between the two treatment groups and can be found in Dr. Winchell's review. In the past year, the majority of subjects in both the varenicline and placebo groups had made no attempt to quit smoking (76.3% vs 81.6%, respectively), and approximately 20% of each group had never attempted to quit. The last serious attempt to quit smoking was more recent for subjects in the varenicline group than in the placebo group (mean values of 469.1 vs 739.3 days prior to Baseline, respectively). The mean Fagerström total score[1] was similar for subjects in the varenicline and placebo groups and consistent with moderate dependence (5.5 vs 5.6, where a higher score indicates greater dependence; range 0-10; 7 is generally considered high). Overall, approximately 37% of subjects smoked their first cigarette of the day within 5 minutes of waking, which is indicative of high dependence. About 60% did not smoke their first cigarette until >30 minutes after waking, which suggests that this is a population of only moderate to low level of dependence. This might argue that the patients identified as "not willing/able to quit abruptly" could well have been "able" to quit abruptly; they were simply not willing.

[1] The Fagerström Test for Nicotine Dependence is a standard instrument for assessing the intensity of physical addiction to nicotine. It contains six items that evaluate the quantity of cigarette consumption, the compulsion to use, and dependence.. The items are summed to yield a total score of 0-10. The higher the total Fagerström score, the more intense is the patient's physical dependence on nicotine. NIDA CTN Common Elements, http://cde.drugabuse.gov/instrument/d7c0b0f5-b865-e4de-e040-bb89ad43202b

Patient disposition is demonstrated in the following table. Study retention was good throughout the study periods with 74% of patients randomized to Chantix and 68% of patients randomized to placebo completing 52 weeks.

Ms. Meaker's Table 1: Patient Disposition

	Varenicline	Placebo
Randomized (FAS)	760 (100%)	750 (100%)
Received Study Treatment	751 (99%)	742 (99%)
Discontinued During Treatment/Reduce-to-Quit Phase (Weeks 1-12)	103 (14%)	131 (17%)
Reason for Discontinuation:		
Adverse Event	9 (1)	10 (1)
Lack of Efficacy	6 (1)	17 (2)
Lost to Follow-up	37 (5)	45 (6)
Subject no longer willing to participate	29 (4)	32 (4)
Other	22 (3)	27 (4)
Discontinued During Treatment/Abstinence Phase (Weeks 13-24)	38 (5%)	52 (7%)
Reason for Discontinuation:		
Adverse Event	3 (<1)	2 (<1)
Lack of Efficacy	0 (0)	10 (1)
Lost to Follow-up	17 (2)	20 (3)
Subject no longer willing to participate	13 (2)	14 (2)
Other	5 (1)	6 (1)
Discontinued During Post-treatment Phase (Weeks 25-52)	51 (7%)	44 (6%)
Reason for Discontinuation:		
Adverse Event	1 (<1)	1 (<1)
Lack of Efficacy	0 (0)	1 (<1)
Lost to Follow-up	22 (3)	16 (2)
Subject no longer willing to participate	12 (2)	13 (2)
Other	16 (2)	13 (2)
Completed Treatment	564 (74%)	513 (68%)
Completed Study	559 (74%)	516 (69%)

Source: Modified from Clinical Study Report Table 9
All percentages are calculated based on Randomized N per group as denominator.

Protocol violations were reviewed by Dr. Arnold and were, overall, not thought to have an impact on the study outcome. No inspections were requested because inspections of several recent similar studies have not identified concerns. However, Dr. Arnold did note that several investigators disclosed substantial payments from Pfizer and requested that Ms. Meaker evaluate the impact of these centers on the outcome.

On both the primary and secondary efficacy endpoints, the varenicline treatment group was statistically significantly better than the placebo treatment group ($p<0.001$). Ms. Meaker was able to replicate the Applicant's results and conducted additional analyses to address a concern with the way missing data was handled in the protocol. Per protocol, missing exhaled CO measurements were imputed as negative "therefore not disqualifying the subject as a responder." This is not the customary approach. Ms. Meaker determined that, for the primary endpoint (weeks 15-24), there were 29 subjects classified as responders who were missing one or more of the CO assessments scheduled for weeks 15, 18, 21, 22, 23, or 24. Of them, only one, in the varenicline group, did not have a confirming CO through Week 24, but did have confirming NUI data recorded for all the weeks in that interval. For the long-term abstinence endpoint (weeks 21-52), 36 subjects were missing one or more CO values scheduled during that timeframes, but all had confirmatory CO assessments after the missing one time points. The imputation of the missing CO measurements did not impact the results.

As described by Dr. Winchell, with patients on treatment for a period of time prior to abstinence, in contrast to earlier studies, it was decided that a grace period of two weeks after the target quit date at Week 12 was reasonable. Protocol-specified secondary endpoints focused on the last month of treatment (Weeks 21-24) and on prolonged abstinence from the last month of treatment through the end of the observation period (Weeks 21-52). The Weeks 15-24 (end of 2 weeks' grace through end-of-treatment) and Weeks 15-52 (end of 2 weeks' grace through end-of-observation) are the more informative rates and should be included. Varenicline was significantly superior to placebo on both of these measures.

As the clinical review team noted an excessive amount of financial compensation to the investigators at five sites (1024, 1035, 1039, 1067, and 1077) additional analyses were conducted excluding the data from these sites. These sites enrolled a total of 125 subjects (62 in varenicline; 63 in placebo). Excluding the data from these sites did not change the conclusions.

Additional explorations by Ms. Meaker revealed that approximately 8% of the Chantix-treated subjects vs. approximately 0.5% (four individuals) of the placebo-treated subjects quit abruptly and met criteria for quit by Week 4. Of these, 66% of the Chantix-treated and half of the placebo-treated subjects ultimately sustained abstinence through the end of the observation period. These represent a small subset of the total successful quitters, suggesting that it is appropriate to conclude that the subjects in this trial who quit smoking mainly did so by gradual reduction and not abruptly, although few appeared to take the entire recommended period to do so.

8. Safety

As noted by Dr. Winchell, the novel safety issue in this study is the greater length of overlap between smoking and Chantix, it is helpful to note that the vast majority of the patients were exposed for periods of time exceeding the 12 week reduction period. Most of the information included in this section has been excerpted from Dr. Winchell's review with little modification.

There was one death. Whether exposure to study drug contributed to the death could not be concluded based on the lack of information submitted.

As noted by Dr. Winchell, through both the treatment and post-treatment follow-up phases, serious adverse events were reported by 34 (4.5%) Chantix-treated and 23 (3.1%) placebo-treated subjects. Only two events were considered study drug related by the investigators; Dr. Arnold reviewed the narratives to evaluate whether they were treatment-emergent and whether a relationship to Chantix could be ruled out. In each treatment arm, there were two cases of depression; in the Chantix arm both cases involved suicidality and one patient made a suicide attempt. In the placebo arm, one patient with depression also reported suicidal ideation. One case of seizure was reported in the Chantix arm. Other events were primarily cardiovascular. These are consistent with known safety concerns related to Chantix. Overall, adverse events leading to permanent discontinuation of study drug occurred at similar rates across study arms (8% of Chantix group vs. 7% of placebo group). This is lower than the 13% of varenicline-treated and 9% of placebo-treated patients that discontinued treatment due to TEAEs in the pivotal trials submitted to the original NDA. Dr. Arnold constructed a table showing reasons for discontinuation. The most common reasons for discontinuation in Chantix-treated patients were nausea and depression. Dr. Winchell was able to reproduce the Sponsor's number of 115 discontinuations. Psychiatric adverse events leading to discontinuation were somewhat more common in the Chantix-treated than the placebo-treated patients; gastrointestinal complaints remain the most common reason for discontinuation in Chantix-treated patients.

Temporary discontinuations or reductions in study drug dose occurred in more Chantix-treated (19%) than placebo-treated (10%) patients. The most common reasons for temporary interruption of study drug were gastrointestinal signs and symptoms. The reasons for dose reduction were overwhelmingly gastrointestinal complaints (nausea, vomiting), followed by sleep disturbances and anxiety symptoms. Common adverse events were consistent with the known safety profile of Chantix.

Because of the boxed warning and general concern for neuropsychiatric adverse events associated with Chantix, this study used the semi-structured interview developed for the dedicated neuropsychiatric adverse event study, the NAEI, and also monitored for emergence of suicidal ideation using the C-SSRS. Cases of serious neuropsychiatric symptoms, including suicidality, were reviewed by Dr. Arnold. There were two SAEs involving suicidality in the Chantix group and one in the placebo group. Pfizer compared the rates of psychiatric events in the RTQ study to the events in the pooled database (the 19-study cohort includes the RTQ study). Higher rates of reporting of depression, anxiety and agitation may reflect the events solicited with the use of the NAEI. These higher rates are seen across both treatment groups. Only agitation appears to be more common in the active treatment group.

Reviews by the Division of Pharmacovigilance in the Office of Surveillance and Epidemiology found support for adding hyperglycemia to the postmarketing adverse reactions and for adding a warning about the risk of somnambulism.

9. Advisory Committee Meeting

No advisory committee meeting was convened for this supplement. The clinical study design and interpretation of the study results did not raise any issues that required additional advice.

10. Pediatrics

The actual dosing of Chantix was not changed with this supplement; just the behavioral instructions for managing the discontinuation of cigarettes. As a result, the requirements of the Pediatric Research Equity Act were not triggered.

11. Other Relevant Regulatory Issues

No inspections were requested because inspections of several recent similar studies have not identified concerns.

12. Labeling

In addition to the information describing the RTQ approach in Dosage and Administration and the new warning for somnambulism agreed upon with the Applicant, the Pregnancy and Lection section of labeling was made consistent with the Pregnancy and Lactation Labeling Rule. The Division of Maternal and Pediatric Health and DAAAP pharmacology/toxicology provided recommendations for this labeling.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action – Approval

- Risk Benefit Assessment

Chantix has been shown effective in assisting patients to stop smoking using when they select a stop date and cease smoking on that day. The current supplement provides support from an adequate and well-controlled clinical trial that Chantix is also effective in assisting patients to stop smoking when they reduce the number of cigarettes they smoke over a period of time. The study design demonstrated that the effect was durable over the course of a year. While there are known risks associated with the use of Chantix, the clinical data submitted to support this supplement do not demonstrate any additional risks with use in the reduce-to-quit setting compared to abrupt cessation.

- Recommendation for Postmarketing Risk Management Activities

Chantix is currently marketed under a Med Guide-only REMS established to manage risk of neuropsychiatric events. No changes to the REMS, other than to update the Med Guide to include the new instructions, are needed.

- Recommendation for other Postmarketing Study Commitments

None.

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

/s/

SHARON H HERTZ
08/12/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021928/S-039

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	June 17, 2016
From	Celia Winchell, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/Supplement#	021928 S039
Applicant	Pfizer, Inc.
Date of Submission	October 13, 2015
PDUFA Goal Date	August 13, 2016
Proprietary Name / Established (USAN) names	CHANTIX (varenicline tartrate) tablet, film coated
Dosage forms / Strength	Oral tablets, 0.5 mg and 1 mg
Proposed Indication(s)	Aid to smoking cessation treatment (approved) Supplement proposes to add new language to Dosing and Administration and Clinical Studies section describing a "reduce-to-quit" regimen, without change to indication
Recommended:	*Approval*

Contents

1. Introduction

This memo serves as the supervisory review for an efficacy supplement submitted to Pfizer's NDA 21928, an aid to smoking cessation treatment marketed as Chantix. The supplement was supported by a single new, randomized, placebo-controlled efficacy trial, Study A3051075, in which patients were instructed in quitting smoking via gradual reduction, rather than abruptly. The primary clinical review was conducted by Sarah Arnold, M.D., and the statistical review was conducted by Kate Meaker, M.S., supervised by David Petullo, Ph.D. The supplement seeks to add this set of directions (a third regimen) to the Dosing and Administration section, and to include a description of the efficacy results to the Clinical Studies section of labeling. Revisions of the labeling to comply with the requirements of the Pregnancy and Lactation Labeling Rule (PLLR) were also included.

2. Background

Varenicline is a high-affinity selective partial agonist of the α4β2 nicotinic receptor, previously designated CP526-555 and developed under IND 58,994, opened on 9/14/1999. The α4β2 nicotinic receptor has been shown to be responsible for the reinforcing properties of nicotine in animal models. Based on the activity at the nicotinic receptor, varenicline could be expected to mitigate withdrawal symptoms and reduce the reinforcing effects of nicotine, leading to efficacy in helping smokers stop smoking. NDA 21,928 was submitted by Pfizer on 11/11/05 and approved on 5/10/06.

The original directions for use instructed patients to set a quit date, initiate Chantix one week *before* the quit date, titrate up to the 1 mg b.i.d. dose over the first week, and then attempt to quit. Treatment continued for 12 weeks. Data from a randomized withdrawal trial in successful quitters also supported a recommendation for a second course of 12 weeks to improve long-term abstinence. Subsequently, the Dosing and Administration section was amended based on a clinical trial of a "flexible approach to setting a quit date," in which patients were instructed to begin taking Chantix without having set a particular quit date, and to choose one between Day 8 and Week 5. Both approaches demonstrated statistically significant effects of Chantix on both initial quit (measured over the last month of treatment) and sustained abstinence (continued to the end of a year of observation, 40 weeks post-treatment). The current submission extends the Dosing and Administration section to allow for an approach which does not require the patient to set a date for quitting abruptly, but instead to gradually reduce smoking over a period of three

months of treatment, and then to continue Chantix for three additional months after ultimately quitting.

This is a significant departure from most recommendations for quitting smoking. There has long been interest in developing "reduce-to-quit" (RTQ) approaches to smoking cessation, and some studies have been attempted using nicotine replacement products with results that are not compelling. Many in the smoking cessation field note that for smokers who are reluctant to quit, the prospect of RTQ is considered an attractive option. Notably, there has been some doubt whether such a regimen would be effective. Behavioral methods involving gradual reduction of smoking ("fading") have not generally been regarded as effective (Lindson-Hawley, 2016). Furthermore, it is also believed that any smoking at all after the "quit date" is associated with a greatly reduced chance of successful abstinence, as evidenced by the similarity in responder rates when previous trials of nicotine replacement therapy (NRT) have been analyzed with respect to "abstinence" vs. "abstinence, slip allowed." It is theorized that as the number of cigarettes per day is reduced, each remaining cigarette smoked is more reinforcing, making the behavioral change more difficult. Because Chantix is thought to make smoking less reinforcing, it may be helpful in facilitating a gradual reduction approach to smoking cessation that may be more appealing to reluctant quitters.

2.1 Original NDA Findings

The initial approval was based on results from 30 completed (24 Phase 1, 8 Phase 2/3) and 3 ongoing clinical studies. The studied population included adult smokers of at least 10 cigarettes/day, generally in good health, with exclusions for laboratory abnormalities, psychiatric conditions, hypertension, significant cardiovascular history (remote history allowable in Phase 3), or other significant medical illnesses.

The main smoking cessation studies in the original NDA were basically similar in design. After initial screening assessments and a baseline visit, subjects were randomized to one of the treatment arms, which included placebo, varenicline (various doses in Phase 2; 1 mg b.i.d. in Phase 3), and, in several studies, Zyban at labeled doses (i.e., 150 mg b.i.d. with initial dose titration). Subjects attended study visits weekly visits during treatment (12 weeks in most studies), and were to quit smoking on treatment day 7. Smoking status was assessed at each visit via self-report (nicotine use inventory) and exhaled carbon monoxide. The protocol also called for provision of an educational booklet on smoking cessation (National Cancer Institute's "Clearing the Air" booklet) and were provided with up to 10 minutes of counseling at each visit following Agency for Healthcare Research and Quality guidelines. Subjects who completed the 12 weeks of the treatment phase (even those who discontinued using study medication but elected to stay in the study) were then followed for an additional 40 weeks with clinic visits at roughly 12 week intervals, supplemented with intervening telephone contacts.
The pre-specified primary endpoint was the 4-week Continuous Quit Rate (CQR) for the last four weeks of treatment (for most studies, Weeks 9 to 12). Subjects were to be classified as responders if they were able to maintain complete abstinence from cigarette smoking and other nicotine use for the last 4 weeks of treatment with end-expiratory exhaled CO measurements ≤ 10 ppm.

In the Phase 2 and 3 studies, varenicline treated patients were more likely to achieve the protocol-specified definition of abstinence than patients treated with placebo or with Zyban in all studies, demonstrating substantial evidence of efficacy and of superiority over existing treatment. The results of two trials designated as pivotal, Study A3051028 ("Study 28") and A3051036 ("Study 36") are shown in the table below alongside the results of the new trials.

In the original NDA submission, the overall exposure to varenicline was adequate to characterize the safety profile and met ICH requirements. The overall safety database included 4690 individuals who were exposed to varenicline, including 456 subjects treated with varenicline 1 mg b.i.d. (the highest proposed marketed dose) for at least 24 weeks, and 112 for 364 days or more. Treatment-related adverse events included nausea, vomiting, flatulence, constipation, insomnia, abnormal dreams, dysgeusia, and increased appetite (leading, in longer-term treatment, to weight gain). Approximately 13% of subjects in short-term studies discontinued due to adverse events, although only nausea, headache, and insomnia accounted for discontinuation in >1% of subjects, and only nausea was clearly a more common cause of treatment discontinuation in active-treated subjects compared to placebo-treated. Varenicline did not have consistent effects on any laboratory parameters, cardiac conduction parameters, or vital sign measurements.

2.2 Special Concerns in This Review

Chantix has been associated with a number of safety issues in the post-market setting, including neuropsychiatric events, cardiovascular events, accidental injury, serious skin reactions, potentiation of alcohol effects, and convulsions. The population studied in this trial was very similar to previously-studied populations in terms of general health, but the regimen involves a longer period of time where patients are instructed to overlap Chantix and smoking; therefore, the reviewer was interested in evaluating whether the adverse event profile was different from the established profile in any significant respect.

3. CMC/Device

No new CMC issues were raised by this supplement.

4. Nonclinical Pharmacology/Toxicology

The pharmacology/toxicology team reviewed the proposed labeling for conformity with the requirements of the PLLR and made appropriate recommendations for revision. No other new pharmacology/toxicology or nonclinical safety issues were raised by this supplement.

5. Clinical Pharmacology/Biopharmaceutics

No new clinical pharmacology/biopharmaceutics information was included in this supplement. The text below, adapted from the approved labeling, summarizes the clinical pharmacology of Chantix:

Varenicline binds with high affinity and selectivity at 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.

Absorption of varenicline is virtually complete after oral administration and systemic bioavailability is ~90%. Cmax occurs within 3-4 hours of administration, T1/2 is approximately 24 hours, and steady-state conditions are reached in 4 days. Bioavailability is unaffected by food or time of day. Plasma protein binding is low and independent of age and renal function. Varenicline undergoes minimal metabolism, with 92% excreted unchanged in the urine. 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.

In subjects with moderate renal impairment, varenicline exposure increased 1.5-fold compared with subjects with normal renal function. In subjects with severe renal impairment (estimated creatinine clearance <30 mL/min), varenicline exposure was increased 2.1-fold. Dose reduction is recommended for patients with renal impairment. Due to the absence of significant hepatic metabolism, varenicline pharmacokinetics should be unaffected in patients with hepatic impairment.

No clinically meaningful pharmacokinetic drug-drug interactions have been identified. In vitro studies demonstrated that varenicline does not inhibit renal transport systems or 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.

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.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Protocol A3051075: A Phase 4, Multi-National, Randomized, Double-Blind, Placebo Controlled Study to Evaluate the Efficacy and Safety of Varenicline Compared to Placebo for Smoking Cessation Through Reduction, Conducted July 19, 2011- July 12, 2013

61 centers in the United States, Canada, Mexico, Europe, Egypt, Japan, Taiwan, and Australia

This supplement included the results of one new efficacy trial, Study A3051075, and sought to add a new set of instructions to the Dosing and Administration section of labeling and a description of the study results to the Clinical Trials section. The trial demonstrated the efficacy of Chantix in helping smokers to quit using a gradual reduction approach, increasing the proportions of

patients able to achieve abstinence at the end of the reduction period and sustain it through the end of treatment (Weeks 15-24), and the proportion of patients able to sustain abstinence to the end of the year (28 weeks of post-treatment follow-up). The table below summarizes the efficacy findings places them beside the findings from the original pivotal trials submitted in support of the NDA for reference. More detailed descriptions of the study (including a discussion of the different efficacy ascertainment windows) and the results follow.

	Chantix	Placebo
Study A3051075	N = 760	N = 750
Continuous Abstinence Weeks 15-24	32%	7%
Continuous Abstinence Weeks 15-52	24%	6%
Study 28	N = 349	N = 344
Continuous Abstinence Weeks 9-12	44%	17%
Continuous Abstinence Weeks 9-52	21%	8%
Study 36	N = 343	N = 340
Continuous Abstinence Weeks 9-12	44%	18%
Continuous Abstinence Weeks 9-52	22%	10%

7.1 Study Design

Study A3051075 was a randomized, double-blind, multicenter study comparing varenicline to placebo in adults trying to quit smoking. The study design, dosing regimen, efficacy endpoints, and analyses were mostly similar to the Phase 3 studies used to support the initial application in 2005. They main difference was in the timing and manner of the attempt to quit smoking. During the first 4 weeks of treatment subjects agreed to reduce the number of cigarettes smoked by at least 50% from baseline; by 8 weeks they would reduce by 50% again (75% from baseline); and at Week 12 the intent was to quit entirely. Treatment with study drug continued through Week 24.

Eligible patients were adult smokers of at least 10 cigarettes/day (on average, over the past year and during the month prior to screening) who were not willing/able to quit smoking within the next month but who were willing to attempt to reduce their smoking to work toward a quit attempt within the next 3 months.

Key exclusion criteria were pregnancy, nursing, psychiatric conditions[1] (those with mild-to-moderate conditions could be included if meeting criteria for stability), substance use disorders, medical conditions (severe COPD, recent significant cardiovascular or cerebrovascular disease, recent cancer, ECG or LFT abnormalities). Disallowed concomitant medications included other smoking cessation aids, as well as some other medications thought to affect or be affected by smoking cessation[1].

Patients were randomly assigned at a 1:1 ratio to treatment with varenicline or placebo. Dosing followed the labeled regimen: 1 week run-in titration (0.5 mg BID for 3 days; 1.0 mg BID for 4

[1] Detailed inclusion and exclusion criteria and excluded medications are listed in Dr. Arnold's review.

days), then increase to 1 mg BID dosing in Week 2 and continued through Week 24. Subjects who had difficulties with tolerability could have the blinded dose lowered temporarily or permanently to 0.5 mg BID. Patients were followed for 28 weeks after treatment (52 weeks total) to assess continued abstinence from smoking. Use of nicotine replacement therapy or other nicotine-containing products was prohibited during the study.

Subjects were instructed to reduce the number of cigarettes smoked by at least 50 percent by the end of the first four weeks of treatment, followed by a further 50 percent reduction from week four to week eight of treatment, with the goal of reaching complete abstinence by 12 weeks. After the initial 12-week reduction phase, subjects continued treatment for another 12 weeks. Clinic visits were scheduled at Week 1, 2, 4, 6, 8, 12, 15, 18, 21, 22, 23, and 24 during the 24-week treatment period, and at Weeks 26, 32, 40, 48 and 52 during the post-treatment period. Phone contact was scheduled at Weeks 3, 5, 7, 10, 14, 16, 20, 28, 36 and 44. Use of cigarettes or other nicotine-containing products was measured using the Nicotine Use Inventory (NUI) at all clinic visits or phone contacts throughout the 52 week study. Exhaled carbon monoxide (CO) was measured at each clinic visit

All participants were to receive up to 10 minutes of smoking cessation counseling in accordance with Agency for Healthcare Research and Quality (AHRQ) guidelines2 or similar local guidelines, at each clinic visit and telephone contact starting with the Baseline visit.

Efficacy was assessed using a Nicotine Use Inventory and end-expiratory exhaled carbon monoxide (exhaled CO) monitoring. The primary and key secondary endpoints were defined based on those measures. The pre-specified primary endpoint was exhaled carbon monoxide (CO)-confirmed 10-week continuous abstinence (CA), with the 10 weeks being counted from weeks 15-24, inclusive, using patient self-reports of cigarette and nicotine use 'since last visit' and CO measurements conducted in the clinic visit. This aligns with previous endpoints which allowed two weeks of "grace" from the scheduled Quit Day (end of Week 12) and continued through the end of dosing. Subjects were to be classified as responders if they were able to maintain complete abstinence from cigarette smoking and other nicotine use for the last 10 weeks of treatment with end-expiratory exhaled CO measurements ≤ 10 ppm.

7.2 Population

Planned enrollment was approximately 1404 subjects randomized 1:1 to each of two treatment arms. A total of 1510 subjects were actually randomized and 1493 received study treatment.

Demographics

Patient characteristics are shown in the tables below (from Dr. Arnold's review).

Demographics

[2] Fiore MC, Jaen CR, Baker TB, et al. Clinical practice guideline; U.S. Department of Health and Human Services, DHHS publication no. (CDC) 88-8406, 2000 referenced.

Dr. Arnold's Table 9: Demographic Characteristics - All Treated Population (Source: Study report, section 11.2, Table 12)

	Varenicline (N = 751)		Placebo (N = 742)	
Age, n (%)	Male (N = 421)	Female (N = 330)	Male (N = 421)	Female (N = 321)
18-44 years	212 (50.4)	152 (46.1)	208 (49.4)	160 (49.8)
45-64 years	189 (44.9)	164 (49.7)	186 (44.2)	146 (45.5)
≥ 65 years	20 (4.8)	14 (4.2)	27 (6.4)	15 (4.7)
Mean (SD)	44.4(11.9)	45 (11.8)	44.7 (12.2)	44 (11.9)
Range	19-78	20-79	18-78	19-73
Race, n (%)				
White	217 (51.5)	254 (77.0)	229 (54.4)	226 (70.4)
Black	20 (4.8)	14 (4.2)	20 (4.8)	27 (8.4)
Asian	129 (30.6)	46 (13.9)	130 (30.9)	47 (14.6)
Other	55 (13.1)	16 (4.8)	42 (10.0)	21 (6.5)
Body Mass Index, kg/m[e]				
Mean (SD)	26.7 (5.0)	26.9 (6.6)	26.9 (5.3)	27.1 (6.7)
Range	17.2-56.2	16.5-64.3	15.8-52.6	16.2-61.6

[a] Subject (b) (6) was assigned to varenicline as a male but is in fact female.
The All Treated population which was the Safety Analysis Set included all subjects who had been randomized and received at least 1 dose, including partial doses of randomized medication.
Body mass index was defined as weight/(height x 0.01)^2.

Smoking history and Fagerström score for Nicotine Dependence for the All-Treated population are displayed in the table below.

Dr. Arnold's Table 1. Smoking History and Fagerström Test for Nicotine Dependence – All Treated Population (Source: Study report, section 11.2.2, Table 13)

	Measure	Varenicline (N=751)	Placebo (N=742)
Age started smoking	Mean (SD)	17.3 (4.32)	17.3 (4.45)
Total years smoked	Mean (SD)	26.7 (12.25)	26.5 (12.17)
Average cigarettes per day			
since started smoking	Mean (SD)	18.6 (8.82)	19.0 (8.54)
In past year	Mean (SD)	10.7 (8.54)	20.7 (8.01)
In past month	Mean (SD)	20.6 (8.44)	20.8 (8.20)
Longest abstinence period, days			
Over lifetime	Mean (SD)	266.4 (695.43)	206.4 (635.10)
In past year	Mean (SD)	3.6 (11.50)	2.7 (9.58)
Last serious quit attempt(days ago)	Mean (SD)	469.1 (1162.97)	739.3 (1698.21)
Lifetime serious quit attempts, Any method[a]			
None	n (%)	129 (17.2)	158 (21.3)
One		189 (25.2)	186 (25.1)
Two		138 (18.4)	108 (14.6)
Three or more		295 (39.3)	290 (39.1)
Serious quit attempts in the past year, Any method			
None	n (%)	573 (76.3)	605 (81.6)
One		137 (18.2)	103 (13.9)
Two		22 (2.9)	18 (2.4)
Three or more		19 (2.5)	15 (2.0)
Nicotine Dependence: Fagerström Test	n Mean (SD) Range	750 5.5 (2.08) 0-10	741 5.6 (2.03) 0-10

The All Treated population which was the Safety Analysis Set included all subjects who had been randomized and received at least one dose, including partial doses, of randomized medication. Percentages were based on the number of subjects with non-missing responses to the given question. [a]Calculated field, which represented the number of quit attempts and/or types used. Abbreviations: N = number of subjects in treatment group; n = number of subjects with the given response; SD = standard deviation.

The groups were similar at baseline with respect to the age they had started smoking, duration of smoking, and number of cigarettes per day.

Notably, in the past year, the majority of subjects in both the varenicline and placebo groups had made no attempt to quit smoking (76.3% vs 81.6%, respectively), and approximately 20%

of each group had never attempted to quit. The last serious attempt to quit smoking was more recent for subjects in the varenicline group than in the placebo group (mean values of 469.1 vs 739.3 days prior to Baseline, respectively).

The mean Fagerström total score was similar for subjects in the varenicline and placebo groups and consistent with moderate dependence (5.5 vs 5.6, where a higher score indicates greater dependence; range 0-10; 7 is generally considered high). Overall, approximately 37% of subjects smoked their first cigarette of the day within 5 minutes of waking, which is indicative of high dependence. About 60% did not smoke their first cigarette until >30 minutes after waking, which suggests that this is a population of only moderate to low level of dependence. This might argue that the patients identified as "not willing/able to quit abruptly" could well have been "able" to quit abruptly; they were simply not willing.

Patient Disposition

Patient disposition is shown in Ms. Meaker's Table 1 below. Subjects could discontinue study treatment but remain in the study; additionally, because of the prolonged post-treatment follow-up observation period, subjects could also complete treatment but not complete the study. Over half of the premature discontinuations in both treatment arms occurred during the first 12 weeks of treatment, the gradual reduction phase. The most common reasons were lack of efficacy, loss to follow-up, and "no longer willing to participate." A review of the tabulated comments suggested that withdrawal of consent occurred primarily for perceived lack of efficacy or belief (sometimes correct) that the patient was in the placebo arm, but also sometimes because the patient had succeeded in quitting smoking. The category did not seem to obscure patients withdrawing due to adverse events.

Ms. Meaker's Table 1: Patient Disposition

	Varenicline	**Placebo**
Randomized (FAS)	760 (100%)	750 (100%)
Received Study Treatment	751 (99%)	742 (99%)
Discontinued During Treatment/Reduce-to-Quit Phase (Weeks 1-12)	103 (14%)	131 (17%)
Reason for Discontinuation:		
Adverse Event	9 (1)	10 (1)
Lack of Efficacy	6 (1)	17 (2)
Lost to Follow-up	37 (5)	45 (6)
Subject no longer willing to participate	29 (4)	32 (4)
Other	22 (3)	27 (4)
Discontinued During Treatment/Abstinence Phase (Weeks 13-24)	38 (5%)	52 (7%)
Reason for Discontinuation:		
Adverse Event	3 (<1)	2 (<1)
Lack of Efficacy	0 (0)	10 (1)
Lost to Follow-up	17 (2)	20 (3)
Subject no longer willing to participate	13 (2)	14 (2)
Other	5 (1)	6 (1)
Discontinued During Post-treatment Phase (Weeks 25-52)	51 (7%)	44 (6%)
Reason for Discontinuation:		
Adverse Event	1 (<1)	1 (<1)
Lack of Efficacy	0 (0)	1 (<1)
Lost to Follow-up	22 (3)	16 (2)
Subject no longer willing to participate	12 (2)	13 (2)
Other	16 (2)	13 (2)
Completed Treatment	564 (74%)	513 (68%)
Completed Study	559 (74%)	516 (69%)

Source: Modified from Clinical Study Report Table 9
All percentages are calculated based on Randomized N per group as denominator.

7.3 Study Conduct

Dr. Arnold identified a number of protocol violations. The most relevant types of protocol violations are those involving enrollment of patients with CO concentration < 10 ppm at baseline (indicating they were not current smokers), and those involving use of prohibited concomitant smoking cessation treatments or nicotine. Four subjects in the varenicline group and two in the placebo group had CO concentrations < 10 ppm. None of them were responders for any of the endpoints; this does not affect interpretation of the study. The use of nicotine replacement, e-cigarettes, or other prohibited smoking cessation products (including non-study varenicline) could also influence the outcome. A total of 51 subjects had violations of this nature. However, by considering the timing of the medication use and the adjudication of the subjects, Dr. Arnold concluded that none of these had an impact on the interpretation of the study.

No inspections were requested because inspections of several recent similar studies have not identified concerns. However, Dr. Arnold did note that several investigators disclosed substantial payments from Pfizer and requested that Ms. Meaker evaluate the impact of these centers on the outcome.

7.4 Statistical Methodologies

The protocol specified analysis of various windows for efficacy ascertainment. As noted above, the primary endpoint was the Continuous Abstinence Rate (CAR) during Weeks 15-24. The primary and secondary efficacy endpoints (CAR at weeks 15-24, 21-24, and 21-52) were tested using a logistic regression model with terms for treatment group and center. In order to preserve the Type I family-wise error rate of 0.05, a fixed-sequence hierarchical closed testing procedure was utilized. The order of testing was 1) the CAR for weeks 15-24; 2) CAR for weeks 21-24; and 3) CAR for weeks 21-52. Each comparison was tested at α=0.05.

7.5 Results and Conclusions

On both the primary and secondary efficacy endpoints, the varenicline treatment group was statistically significantly better than the placebo treatment group ($p<0.001$). Table 3 presents the Applicant's results, along with additional endpoints of interest to the clinical review team. Ms. Meaker was able to replicate the Applicant's results.

Additionally, Ms. Meaker addressed a concern with the way missing data was handled in the protocol. Per protocol, missing exhaled CO measurements were imputed as negative "therefore not disqualifying the subject as a responder." This is not the customary approach. Ms. Meaker determined that, for the primary endpoint (weeks 15-24), there were 29 subjects classified as responders who were missing one or more of the CO assessments scheduled for weeks 15, 18, 21, 22, 23, or 24. Of them, only one, in the varenicline group, did not have a confirming CO through Week 24, but did have confirming NUI data recorded for all the weeks in that interval. For the long-term abstinence endpoint (weeks 21-52), 36 subjects were missing one or more CO values scheduled during that timeframes, but all had confirmatory CO assessments after the missing one timepoints. The imputation of the missing CO measurements did not impact the results.

The tables below include various time windows for efficacy ascertainment. Historically, for smoking cessation, six-week trials were considered conventional, and the ascertainment window was set at weeks 2-6, somewhat arbitrarily. This was meant to allow a two-week "grace period" after the scheduled quit day.

However, although this trial duration was appropriate for nicotine replacement products, which were assumed to treat a self-limiting condition (acute nicotine withdrawal), more recently, the clinical approach to smoking cessation treatment has been moving toward viewing the disorder of tobacco dependence as a chronic, relapsing condition, and a longer-term approach to treatment has been more common. A "last four weeks of treatment" window was used in initial varenicline studies, which were 12 weeks in duration. However, the Division's thinking has evolved as longer and longer treatment durations have been proposed, sometimes resulting in a grace period of many months and an efficacy ascertainment period of four weeks. Ultimately, the concept of "abstinence throughout treatment following a pharmacologically-justified grace period" has been recommended to sponsors of ongoing development programs. The primary endpoint, CAR 15-24, follows this principal, allowing 2 weeks of grace after the target quit date at Week 12. Protocol-specified secondary endpoints focused on the last month of treatment (Weeks 21-24) and on prolonged abstinence from the last month of treatment through the end of the observation period (Weeks 21-52). However, because patients have already had 12 weeks of pharmacologic and behavioral treatment prior to the planned quit date, as well as 2 weeks of grade, in this reduce-to-quit study, there does not seem to be a strong argument for applying an *additional* prolonged grace period after the protocol-specified quit date. The secondary window of "last four weeks of treatment" (Weeks 21-24) was included in the protocol but on further consideration it does not seem justified. Pfizer has proposed inclusion of this rate in the label but it does not add additional information and should not be included. Instead, the Weeks 15-24 (end of 2 weeks' grace through end-of-treatment) and Weeks 15-52 (end of 2 weeks' grace through end-of-observation) are the more informative rates and should be included. Varenicline was significantly superior to placebo on both of these measures.

Ms. Meaker's Table 3: Efficacy Analysis Results

All Subjects	Varenicline	Placebo	Odds Ratio (95% CI)	p-value
Primary:				
Continuous Abstinence Rate Weeks 15-24	244/760 32%	52/750 7%	8.7 (6.1, 12.5)	p<0.001 [a]
Continuous Abstinence Rate Weeks 15-52	182/760 24%	45/750 6%		
Secondary:				
Continuous Abstinence Rate Weeks 21-24	287/760 38%	94/750 13%	5.7 (4.2, 7.6)	p<0.001 [a]
Secondary:				
Continuous Abstinence Rate Weeks 21-52	205/760 27%	74/750 10%	4.0 (2.9, 5.5)	p<0.001 [a]
Reduce by 50% from Baseline to Week 4	485/760 64%	278/750 37%		
Reduce by 75% from Baseline to Week 8	450/760 59%	225/750 30%		
Reduce by 100% from Baseline to Week 12 (Quit by Week 12)	224/760 29%	48/750 6%		

Source: Modified from Clinical Study Report Table 15

[a] The odds ratios and p-values were obtained from a logistic regression model including the main effects of treatment and pooled center.

Since the clinical review team noted an excessive amount of financial compensation to the investigators at five sites (1024, 1035, 1039, 1067, and 1077) additional analyses were conducted excluding the data from these sites. These sites enrolled a total of 125 subjects (62 in varenicline; 63 in placebo). Excluding the data from these sites did not change the conclusions.

Given the longstanding question of whether quitting by gradual reduction is or is not a suitable and effective method of quitting smoking, we considered it important to determine whether the patients who quit smoking in this trial actually did so gradually. The primary outcome can be seen as a composite of successful abrupt quitters and gradual quitters. As with other composite endpoints, it is necessary to explore the effect of the drug on components of the composite before allowing a new claim. Additional explorations by Ms. Meaker revealed that approximately 8% of the Chantix-treated subjects vs. approximately 0.5% (four individuals) of the placebo-treated subjects quit abruptly and met criteria for quit by Week 4. Of these, 66% of the Chantix-treated and half of the placebo-treated subjects ultimately sustained abstinence through the end of the observation period. These represent a small subset of the total successful quitters, suggesting that it is appropriate to conclude that the subjects in this trial who quit smoking mainly did so by gradual reduction and not abruptly, although few appeared to take the entire recommended period to do so.

The findings in the placebo group may be interpreted as confirmation that the RTQ method is not a very good method by itself. Although the population was selected on the basis of being "unwilling or unable" to quit abruptly, it is not clear why the participants felt unwilling or unable to quit; they were, overall a fairly low-dependency group; 60% had few, sometimes no, previous quit attempts. Nonetheless, the overall initial quit rate was low compared to the historical placebo rate for other Chantix studies. It is difficult to know whether this represents the reluctance or recalcitrance of the population, the lack of effectiveness of the method, or the differences in efficacy ascertainment window timing and duration. However, because RTQ is typically recommended only to those who self-identify as unwilling to attempt abrupt cessation, the findings are relevant in either case. Notably, the Chantix-attributable (placebo-subtracted) rate of initial quitting success is about the same in this study as in previous studies in more quit-ready smokers. The gradual reduction method should probably not be recommended to smokers who feel they are ready or able to quit abruptly, whether with or without pharmacologic support; however, for those who are willing to attempt cessation only on a gradual basis, the method works much better with Chantix than without it.

8. Safety

The extent of exposure to Chantix in this study is shown in Dr. Arnold's Table 17, below. Because the novel safety issue in this study is the greater length of overlap between smoking and Chantix, it is helpful to note that the vast majority of the patients were exposed for periods of time exceeding the 12 week reduction period.

Dr. Arnold's Table 17. Duration of Treatment - All Treated Population

Number of Subjects	Varenicline (N=751)	Placebo (N=742)
Duration Category (Days)		
≤1	2	1
2-7	6	7
8-14	22	21
15-28	26	15
29-60	55	80
61-90	24	48
91-120	31	37
121-150	47	45
≥151	538	488
Median Duration	167.0	166.0
Range	1-204	1-189

All Treated Population (N) included all subjects who have been randomized and received at least 1 dose, including partial doses, of randomized study medication.
NOTE: The duration was defined as the total number of dosing days from the first to and including the last day of each treatment.

Pfizer also included comparisons to the pooled safety database from all completed controlled trials, a cohort of 18 studies comprising 5,072 varenicline-treated and 3,449 placebo-treated patients. Analyses comparing certain key adverse event types between the present study and the 18-study cohort were examined to explore for indicators of different adverse event profiles in this population.

8.1 Deaths

One death was reported, which was assessed by the investigator as unrelated to study drug. The original narrative provided no information about the circumstances or nature of the death, but additional information supplied at the Division's request revealed that the patient had been found dead at home of unknown causes after neighbors reported him missing for several days. He had attended the Baseline and Week 1 visits and received a supply of study drug, but missed the Week 2 visit, and the death was assumed to have happened some time between the two visits. No autopsy, toxicology, or medical records were apparently available. A relationship to Chantix cannot be ruled out in this case. Chantix has been previously associated with cardiovascular disease and seizures, both possible causes of sudden death; however, it is not possible to determine whether Chantix played a role in this death.

8.2 SAEs

Overall, through both the treatment and post-treatment follow-up phases, Serious Adverse Events were reported by 34 (4.5%) Chantix-treated and 23 (3.1%) placebo-treated subjects. Only two events were considered study drug related by the investigators; Dr. Arnold reviewed the narratives to evaluate whether they were treatment-emergent and whether a relationship to Chantix could be ruled out. In each treatment arm, there were two cases of depression; in the Chantix arm both cases involved suicidality and one patient made a suicide attempt. In the placebo arm, one patient with depression also reported suicidal ideation. One case of seizure was reported in the Chantix arm. Other events were primarily cardiovascular. These are consistent with known safety concerns related to Chantix.

Dr. Arnold's brief summary of key events is shown below.

Table 2. Serious Adverse Events-All Treated Population (review of Pfizer's Table 14.3.2.2)

Varenicline				Placebo			
Subject	Adverse Event	Brief Description	Onset (Trial Day)	Subject	Adverse Event	Brief Description	Onset (Trial Day)
36 yo M (b) (6)	Depression Suicidal ideation	10 days after start of study drug, subject reported sxs of depression, 10 days later, depression worsened to Suicidal ideation and subject was hospitalized for 10 days. Study drug was continued (106 days treatment)until subject withdrew from study, was "unwilling to participate"	21	50 yo F (b) (6)	Depression, hallucinations, Subarachnoid Hemorrhage	Subject experienced depression one month after study drug started, study drug continued, 2 months into study, subjected experienced hallucination, resolved one day later, continued study drug, several weeks later, subject had ruptured cerebral aneurysm, study drug was withdrawn after 123 days of treatment.	110
40 yo F (b) (6)	Suicide attempt	Subject had h/o depression on escitalopram, while on study drug for 35 days, she had migraine, treated as outpatient, study drug continued. Subject's depression worsened 3 months later, and evolved into suicidal ideation and intentional self-injury, suicide attempt, taking extra alprazolam (had from prior treatment). Study drug was withdrawn after 145 days of treatment.	35	45 yo F (b) (6)	Depression, suicidal ideation, Alcoholism	Subject had moderate depression one month into the study, drug was continued. At week 8, subject expressed non-specific active suicidal thoughts without plan, which persisted through week 12, when subject was hospitalized for alcoholism, study drug was discontinued at the time of hospitalization.	79
30 yo M (b) (6)	Seizure	h/o insomnia, being treated with brotizolam and flunitrazepam, amobarbital, and perphenazine. Subj had seizure, had evaluation at hospital, was treated for seizure, study drug continued for 166 days.	132	33 yo F (b) (6)	Vertigo and Vomiting	Subject experienced severe vertigo and vomiting, was hospitalized for 4 days, receiving IV fluids. Study drug withdrawn, subject withdrawn from study	85
51 y/o M (b) (6)	Hypertensive crisis	Subject was hospitalized for hypertensive crisis for 6 days, study drug continued. Subject was also treated for alcohol abuse with potassium, thiamine and carbamazepine, and psychotherapy, study drug was continued.	119 81	47 yo M (b) (6)	Myocardial Infarction	Subject sustained MI, was hospitalized for angioplasty, stent placement, subject permanently discontinued study	35
51 yo M (b) (6)	Aortic aneurysm	10 days into study, pt had presyncopal event requiring evaluation, no change in drug dose. Drug discontinued day 157 due to aortic aneurysm rupture.	10	53 yo F (b) (6)	Myocardial Infarction	Subject experienced myocardial infarction , was hospitalized for treatment, drug was permanently discontinued after 99 days of treatment.	99

45 yo M (b) (6)	Supraventricular tachycardia	Supraventricular tachycardia requiring adenosine, no change in drug dose.	53	32 yo F (b) (6)	Diabetes	Subject had hypertension, inadequate control of diabetes, and a diabetic foot ulcer, study drug temporarily stopped, events resolved and study drug was re-started for total treatment of 141 days.	33
57 yo M (b) (6)	Hypertensive crisis	Subject had chronic HTN controlled on metoprolol, 2 episodes of hypertensive crisis, had to add 2 more medications, study drug not withdrawn, was taken for 151 days. Pt withdrew from study during follow-up phase, "no longer willing to participate"	155	67 yo F (b) (6)	Peripheral artery disease	Subject was hospitalized for peripheral arterial disease, had angioplasty, subject permanently discontinued study after 84 days of treatment.	85
66 yo M (b) (6)	Angina pectoris	Subject had episode of angina, treated with NTG, and coronary artery stent. Study drug withdrawn at day 144.	133	42 yo F (b) (6)	Ileus	Subject with h/o GERD, esophageal neoplasm, had ileus, which was treated and condition resolved 6 days later, no action taken with study drug.	112
58 yo M (b) (6)	Pancreatic cyst	pancreatic cyst, MRI confirmed benign pancreatic neoplasm, requires pancreatin for pancreatic insufficiency, also had panic attack, study drug withdrawn	95	34 yo M (b) (6)	Chest pain	Chest pain due to lower respiratory tract infection, was hospitalized and treated. Drug was not withdrawn.	150
47 yo M (b) (6)	Gastritis	Subject with h/o GERD, on omeprazole. After 20 days on study drug, pt had gastritis, study drug dose was decreased. Pt had second episode of gastritis, study drug was discontinued after 135 days of treatment.	139	42 yo M (b) (6)	Costochondritis	2 months into the study, subject experienced chest wall pain and mild bronchitis, which resolved with antibiotics. No action taken with drug. Treated for 172 days.	146
57 yo F (b) (6)	Unstable angina, Chest pain, musculoskeletal	musculoskeletal chest pain and unstable angina with anxiety, hospitalized for work-up, study drug discontinued	120	44 yo M (b) (6)	Traumatic injuries (MVA)	Subject sustained pneumothorax, chest contusion and rib fracture in traffic accident, for which he was hospitalized. Subject's daughter died during the study, and he discontinued the study for reasons of bereavement after 100 days of treatment.	64

8.3 Discontinuations and Dose Reductions

Overall, adverse events leading to permanent discontinuation of study drug occurred at similar rates across study arms (8% of Chantix group vs. 7% of placebo group). This is lower than the 13% of varenicline-treated and 9% of placebo-treated patients that discontinued treatment due to TEAEs in the pivotal trials submitted to the original NDA.

Dr. Arnold constructed a table showing reasons for discontinuation. The most common reasons for discontinuation in Chantix-treated patients were nausea and depression. Because of a discrepancy between the numbers of discontinuations reported in her table and that in Pfizer's study report, I conducted the analysis from the submitted datasets reducing the events to one event per action per patient and was able to reproduce the Sponsor's number of 115 discontinuations. I tabulated the reasons for discontinuation by HLGT to group like terms together without duplicating patients and the events leading to discontinuation in two or more patients are shown below. Psychiatric adverse events leading to discontinuation were somewhat more common in the Chantix-treated than the placebo-treated patients; gastrointestinal complaints remain the most common reason for discontinuation in Chantix-treated patients.

Adverse Events Leading to Study Drug Discontinuation

SOC	HLGT	Varenicline N =751		Placebo N - 742	
Cardiac disorders	Coronary artery disorders	1	0.1%	2	0.3%
Ear and labyrinth disorders	Inner ear and VIIIth cranial nerve disorders	0	0.0%	3	0.4%
Gastrointestinal disorders	Gastrointestinal signs and symptoms	18	2.4%	2	0.3%
General disorders and administration site conditions	General system disorders NEC	6	0.8%	5	0.7%
Metabolism and nutrition disorders	Appetite and general nutritional disorders	0	0.0%	2	0.3%
Nervous system disorders	Headaches	4	0.5%	2	0.3%
	Neurological disorders NEC	5	0.7%	3	0.4%
Psychiatric disorders	Anxiety disorders and symptoms	6	0.8%	3	0.4%
	Depressed mood disorders and disturbances	8	1.1%	7	0.9%
	Mood disorders and disturbances NEC	2	0.3%	0	0.0%
	Personality disorders and disturbances in behaviour	2	0.3%	0	0.0%
	Psychiatric disorders NEC	0	0.0%	2	0.3%

	Sleep disorders and disturbances	3	0.4%	7	0.9%
	Suicidal and self-injurious behaviours NEC	2	0.3%	2	0.3%
Skin and subcutaneous tissue disorders	Epidermal and dermal conditions	3	0.4%	1	0.1%
Skin and subcutaneous tissue disorders	Skin appendage conditions	2	0.3%	0	0.0%

Temporary discontinuations or reductions in study drug dose occurred in more Chantix-treated (19%) than placebo-treated (10%) patients. The most common reasons for temporary interruption of study drug were gastrointestinal signs and symptoms. The reasons for dose reduction were overwhelmingly gastrointestinal complaints (nausea, vomiting), followed by sleep disturbances and anxiety symptoms. Labeling for Chantix includes language that explains to the patient that the dose may be reduced for complaints of nausea; efficacy at the 0.5 mg b.i.d. dose was demonstrated in the pre-marketing studies so dose reductions for nausea are not expected to result in lack of efficacy.

Compared to the experience in the pooled dataset, a higher proportion of both varenicline and placebo subjects in this study had AEs leading to dose reduction or temporary discontinuations compared to the 2 pooled cohorts (all-causality AEs: varenicline: 19.2% RTQ Study vs 8.2% 18-Study cohort; placebo: 9.7% vs 4.7%). Because the rates are higher in both the active and placebo arms, a plausible explanation for this higher proportion of AEs leading to dose reduction or temporary discontinuation in this study is the doubling of the treatment duration and consequently, of the observation period, to 24 weeks in this study versus 12 weeks or less in 17 of the 18 studies included in the 18-study cohort. In the pre-marketing database, a long-term safety study had a similarly elevated discontinuation rate due to AEs of 28% in varenicline-treated subjects vs 10% for placebo. However, in that study, the onset of adverse events was generally within the first four weeks of treatment. This suggested that discontinuation may not be attributable to new-onset adverse events observed during long-term treatment, but due to the persistence of bothersome effects such as nausea and abnormal dreams, which may be tolerated during the course of a three-month treatment but which patients are unwilling to endure for longer periods of time.

8.4 Common Adverse Events

The overall profile of common adverse events was similar in this study to the established AE profile. I generated a tabulation of treatment-emergent events at the HLGT level occurring in at least 5% of Chantix-treated subjects and more frequently than in placebo and confirmed that these are the same types of events already well-established as drug-related, notably gastrointestinal symptoms (nausea, vomiting, dyspepsia, constipation) and sleep disturbances (insomnia, abnormal dreams). Depression/depressed mood were not, overall, more common in Chantix-treated than placebo-treated patients in this study.

8.5 Special Safety Topics

This study used the semi-structured interview developed for the dedicated neuropsychiatric adverse event study, the NAEI, and also monitored for emergence of suicidal ideation using the C-SSRS. Cases of serious neuropsychiatric symptoms, including suicidality, were described in the SAE section above. There were two SAEs involving suicidality in the Chantix group and one in the placebo group.

Pfizer compared the rates of psychiatric events in the RTQ study to the events in the pooled database (the 19-study cohort includes the RTQ study). Higher rates of reporting of

depression, anxiety and agitation may reflect the events solicited with the use of the NAEI. These higher rates are seen across both treatment groups. Only agitation appears to be more common in the active treatment group.

Table 3. Psychiatric SOC by HLGT with PTs reported by ≥1% in either treatment group in any cohort.

	Reduce-to-Quit Study		18-Study Cohort		19-Study Cohort	
	Var N=751	Pbo N=742	Var N=5,072	Pbo N=3,449	Var N=5,823	Pbo N=4,191
	number (%) of subjects					
Psychiatric SOC	**293 (39.0)**	**215 (29.0)**	**1,615 (31.8)**	**808 (23.4)**	**1,908 (32.8)**	**1,023 (24.4)**
High Level Group Term Preferred Term						
Adjustment disorders (including subtypes)	**0**	**4 (0.5)**	**1 (<0.1)**	**2 (0.1)**	**1 (<0.1)**	**6 (0.1)**
Anxiety disorders and symptoms	**79 (10.5)**	**85 (11.5)**	**253 (5.0)**	**206 (6.0)**	**332 (5.7)**	**291 (6.9)**
Agitation	20 (2.7)	14 (1.9)	52 (1.0)	32 (0.9)	72 (1.2)	46 (1.1)
Anxiety	52 (6.9)	65 (8.8)	150 (3.0)	141 (4.1)	202 (3.5)	206 (4.9)
Nervousness	10 (1.3)	9 (1.2)	29 (0.6)	24 (0.7)	39 (0.7)	33 (0.8)
Changes in physical activity	**6 (0.8)**	**12 (1.6)**	**46 (0.9)**	**31 (0.9)**	**52 (0.9)**	**43 (1.0)**
Restlessness	6 (0.8)	11 (1.5)	43 (0.8)	31 (0.9)	49 (0.8)	42 (1.0)
Cognitive and attention disorders and disturbances	**0**	**0**	**2 (<0.1)**	**3 (0.1)**	**2 (<0.1)**	**3 (0.1)**
Communication disorders and disturbances	**0**	**0**	**1 (<0.1)**	**1 (<0.1)**	**1 (<0.1)**	**1 (<0.1)**
Deliria (including confusion)	**2 (0.3)**	**1 (0.1)**	**4 (0.1)**	**2 (0.1)**	**6 (0.1)**	**3 (0.1)**
Depressed mood disorders and disturbances	**58 (7.7)**	**61 (8.2)**	**179 (3.5)**	**108 (3.1)**	**237 (4.1)**	**169 (4.0)**
Depressed mood	26 (3.5)	27 (3.6)	67 (1.3)	37 (1.1)	93 (1.6)	64 (1.5)
Depression	25 (3.3)	35 (4.7)	98 (1.9)	61 (1.8)	123 (2.1)	96 (2.3)
Dissociative disorders	**1 (0.1)**	**1 (0.1)**	**8 (0.2)**	**5 (0.1)**	**9 (0.2)**	**6 (0.1)**
Disturbances in thinking and perception	**1 (0.1)**	**2 (0.3)**	**21 (0.4)**	**10 (0.3)**	**22 (0.4)**	**12 (0.3)**
Eating disorders and disturbances	**1 (0.1)**	**0**	**1 (<0.1)**	**0**	**2 (<0.1)**	**0**
Manic and bipolar mood disorders and disturbances	**0**	**0**	**4 (0.1)**	**1 (<0.1)**	**4 (0.1)**	**1 (<0.1)**
Mood disorders and disturbances NEC	**52 (6.9)**	**40 (5.4)**	**347 (6.8)**	**206 (6.0)**	**399 (6.9)**	**246 (5.9)**
Irritability	39 (5.2)	30 (4.0)	255 (5.0)	164 (4.8)	294 (5.0)	194 (4.6)
Personality disorders and disturbance in behaviour	**14 (1.9)**	**12 (1.6)**	**23 (0.5)**	**9 (0.3)**	**37 (0.6)**	**21 (0.5)**
Hostility	8 (1.1)	4 (0.5)	6 (0.1)	1(<0.1)	14 (0.2)	5 (0.1)
Psychiatric and behavioral symptoms NEC	**0**	**0**	**1 (<0.1)**	**2 (0.1)**	**1 (<0.1)**	**2 (<0.1)**
Psychiatric disorders NEC	**5 (0.7)**	**3 (0.4)**	**24 (0.5)**	**19 (0.6)**	**29 (0.5)**	**22 (0.5)**
Schizophrenia and other psychotic disorders	**0**	**0**	**2 (<0.1)**	**1 (<0.1)**	**2 (<0.1)**	**1 (<0.1)**

Sexual dysfunctions, disturbances and gender identity disorders	**2 (0.3)**	**4 (0.5)**	**29 (0.6)**	**17 (0.5)**	**31 (0.5)**	**21 (0.5)**
Sleep disorders and disturbances	**212 (28.2)**	**134 (18.1)**	**1224 (24.1)**	**468 (13.6)**	**1436 (24.7)**	**602 (14.4)**
Abnormal dreams	86 (11.5)	43 (5.8)	494 (9.7)	125 (3.6)	580 (10.0)	168 (4.0)
Initial insomnia	15 (2.0)	9 (1.2)	37 (0.7)	22 (0.6)	52 (0.9)	31 (0.7)
Insomnia	80 (10.7)	51 (6.9)	620 (12.2)	261 (7.6)	700 (12.0)	312 (7.4)
Middle insomnia	17 (2.3)	11 (1.5)	50 (1.0)	15 (0.4)	67 (1.2)	26 (0.6)
Nightmare	13 (1.7)	5 (0.7)	54 (1.1)	22 (0.6)	67 (1.2)	27 (0.6)
Sleep disorder	37 (4.9)	29 (3.9)	173 (3.4)	71 (2.1)	210 (3.6)	100 (2.4)
Somatoform and factitious disorders	**0**	**0**	**0**	**1 (<0.1)**	**0**	**1 (<0.1)**
Suicidal and self-injurious behaviours NEC	**1 (0.1)**	**4 (0.5)**	**9 (0.2)**	**13 (0.4)**	**10 (0.2)**	**17 (0.4)**

Source: Pfizer's ISS Table 23

A few post-marketing cases of hepatic injury have been reported associated with Chantix. Pfizer analyzed the SMQ for drug-related hepatic injury and identified two cases of interest, but further information provided by Pfizer did not allow for full evaluation. It appears the adverse event coding for these events may not have been appropriate. However, ongoing monitoring of hepatic events in the post-marketing reports is warranted.

8.6 Vital Signs, Laboratory Assessments, ECGs

The study did not include routine assessments of laboratory values or ECGs. No notable differences in vital signs between Chantix-treated and placebo-treated groups were seen.

8.7 DPV Reviews

Two recently-completed reviews by the Division of Pharmacovigilance II address topics that were identified during reviews of previous supplements and PSURs.

8.6.1 Somnambulism

Martin Pollack, PharmD., conducted a review of post-marketing reports of somnambulism. He identified 167 unique cases of somnambulism and selected the 61 cases in which harmful or potentially harmful consequences were described. In most cases, the harmful activity occurred outside of the patient's bed and a few occurred within the bed; amnesia was present in 18 of the 61 cases. The most common harmful incidences (decreasing rank) were falls, assaults, automobile operation, and starting fire/getting burned. About half of the cases also reported abnormal dreams/nightmares (both labeled).

Positive dechallenge and event onset time (median 3 weeks) support a causal role for varenicline. In three cases, confounding factors (prior somnambulism occurrence, psychiatric history or concurrent psychotherapeutics and concomitant alcohol) were absent. Varenicline can be considered possibly contributory in the remainder of the cases, which had one or more or of the above confounders or did not provide sufficient information.

DPV recommended that somnambulism be added to the Warnings and Precautions section of labeling. Whether this is best accomplished in the context of this supplement or via a separate Safety Labeling Change is under discussion at this time.

8.6.2 Hyperglycemia

Laurelle Cascio, Pharm.D., and Jane Gilbert, M.D., conducted a review of cases of hyperglycemia and diabetes associated with Chantix. At approval "diabetes mellitus" and "hypoglycemia" were added as infrequent events in the Adverse Reactions section. However, hyperglycemia and diabetes cases continue to be reported.

DPV reviewed FAERS and the published literature, and also consulted the Predictive Safety Team who offered a possible mechanistic basis for an effect of varenicline on glycemic control. They noted that

> Varenicline is a partial agonist on nicotinic acetylcholine receptors (nAChR) and its pharmacologic activity as a smoking cessation aid is primarily through competitive binding with nicotine to α4β2-containing nAChRs in the brain, with higher affinity for the desensitized (non-ion conducting) state of the receptor. nAChRs are involved in both parasympathetic (stimulatory) and sympathetic (inhibitory) nervous system control of insulin secretion from the pancreas, acting at preganglionic and intraganglionic fibers. High affinity binding by varenicline to the desensitized state of nAChRs could potentially inhibit either insulin or glucagon secretion, leading to either hyperglycemia or hypoglycemia. Varenicline is also a full agonist on the ganglionic form of nAChRs (α3β4) although it is not known if α3β4-AChR activation by varenicline can occur at clinically relevant doses and impact glycemic control. The activity of varenicline on nAChRs may also be impacted by chronic nicotine use which can increase nAChR numbers on the surfaces of cells and also cause changes in subunit stoichiometry, which affects binding affinity.
>
> Nicotine use is itself associated with an increased risk of hyperglycemia and hypoglycemia in non-diabetics and diabetics. The alteration of insulin sensitivity by chronic nicotine use can produce hypoglycemia in diabetics who quit smoking, which could account for part of the association of varenicline use with this adverse effect.
>
> In summary, there does appear to be a mechanistic basis for varenicline and hyperglycemia/diabetes mellitus and hypoglycemia. The mechanism may involve partial agonist activity on nicotinic acetylcholine receptors of the parasympathetic and sympathetic nervous systems that mediate cholinergic control of pancreatic function.

DPV's FAERS search retrieved 955 reports; 851 for hyperglycemia/new onset diabetes and 104 for hypoglycemia. In light of the large number of reports for hyperglycemia/new onset diabetes, a subset of 186 cases, including all death cases and a random sample of each other serious outcome were reviewed hands-on. After applying a case definition, 39 cases formed the case series, including 27 cases of hyperglycemia/diabetes and 12 of hypoglycemia.

The reviewers noted that

> Though we identified 27 FAERS cases describing hyperglycemia/diabetes mellitus and 12 FAERS cases describing hypoglycemia, including 8 with a positive dechallenge, it is difficult to conclude with certainty that there is a causal association between the drug and these events. There are numerous reasons why this conclusion is difficult to reach.

First, nicotine is known to be independently associated with an increased risk of hyperglycemia and hypoglycemia in non-diabetics and diabetics. This is due to alteration of insulin resistance through chronic nicotine use which can result in hypoglycemia in diabetics who quit smoking.[6, 7]
Additionally, cessation of smoking can change the pharmacokinetics of drugs used to treat diabetes, which may alter blood glucose concentration.[8] Therefore, the act of smoking cessation may, in itself, promote hypoglycemia with or without the use of varenicline. Second, it is inherently difficult to identify a safety signal for adverse events with a high background rate using data from a spontaneous reporting system (e.g., FAERS). Many individuals will experience the outcome of interest (incident diabetes or blood glucose changes) without exposure to the drug, making it dubious to conclude any association is causal. Finally, when patients stop smoking, patients may consume more calories and gain weight.Weight gain, even modest amounts, following smoking cessation may increase the risk of developing diabetes in some patients, irrespective of varenicline use.

The FAERS cases and known pharmacologic activity of varenicline provide some support for a possible association between varenicline and hyperglycemia, diabetes mellitus, and hypoglycemia. Diabetes mellitus and hypoglycemia are already listed as adverse events in product labeling, and it is reasonable to also include hyperglycemia. However, due to the high background rate of diabetes in the general population as well as possible confounding by drug- metabolism changes, underlying or unrecognized diabetes, and changes in diet, it is difficult to confidently assert there is a compelling safety signal.

The reviewers recommended that hyperglycemia be added to the post-marketing safety section of labeling.

9. Advisory Committee Meeting

None

10. Pediatrics

No new pediatric information was submitted. Pfizer is completing pediatric studies as requested in a Pediatric Written Request.

11. Other Relevant Regulatory Issues

Financial disclosures included with these applications revealed a number of investigators receiving substantial financial compensation. However, analysis of the efficacy data with all potentially conflicted sites removed did not change the conclusions.

12. Labeling

Pfizer proposed to add a description of this study to the Clinical Trials section, and to re-order some of the information to group studies in generally healthy populations together (e.g., the flexible quit date study, the retreatment study, and this study). Additionally, a reference to the gradual reduction option was proposed for inclusion in the Dosage and Administration section and the Patient Counseling and MedGuide sections. Finally, language in the Adverse Reactions section was proposed expressing that the adverse event profile in this study was similar to the pre-marketing adverse event profile displayed in the tables. In general, these proposals were accepted, with editorial changes meant to convey that this method could be recommended to patients who are sure they are not ready to quit right away. Additional detail on the directions for the gradual reduction method were also added.

12.1 Pregnancy and Lactation Labeling

Pfizer's proposed changes to the Pregnancy and Lactation sections of labeling were reviewed by the DAAAP pharmacology/toxicology team and by the Division of Pediatric and Maternal Health (DPMH). The sections were restructured to be consistent with the PLLR format.

The pharmacology/toxicology team accepted the proposed non-clinical language in large part, and added information about maternal toxicity.

Pfizer is collecting information on the use of varenicline in pregnancy as part of a post-market study. DPMH reviewed pregnancy data including a published review of 23 pregnancies, one case report, and interim PMR data from the Swedish and Danish birth registers, and determined that it was not possible to draw any conclusions on the safety of varenicline in pregnancy. However, they noted the occurrence of 3 ventricular septal defects (VSDs) out of 12 major malformations in the varenicline exposed cohort, and noted that a potential safety signal may be emerging and will need to be monitored. At the present time, DPMH recommended not adding any human data to labeling. The PMR data will be re-assessed following submission of the final study report, which is anticipated to be submitted in September 2016. Consideration of addition of these data to labeling can be assessed at that time.

Noting that the perinatal risks associated with smoking are well characterized, DPMH felt it would be appropriate to add this information to Clinical Considerations, under the Disease-associated maternal and/or embryo/fetal risk subheading. DPMH also recommended including language about the risks orofacial clefts related to smoking. Although the risks of smoking are well-known, less is known about the risks of Chantix and which of the risks of smoking could be reduced via use of Chantix. There is overlap between the effects of Chantix and the effects of nicotine. Because there are no data that support that use of Chantix decreases smoking-associated risk during pregnancy, there was consensus that the following statement should be added: "It is not known whether quitting smoking with Chantix during pregnancy reduces these risks."

Noting that there are no data to inform the safety of varenicline in the breastfed infant, DPMH recommended including this statement:

"The lack of clinical data during lactation precludes a clear determination of the risk of CHANTIX to an infant during lactation; however the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for CHANTIX and any potential adverse effects on the breastfed child from CHANTIX or from the underlying maternal condition."

In addition, DPMH recommended the addition of advice to monitor breastfed infants for specific labeled adverse events that might be detected in infants. Specifically, seizures and vomiting were identified. Because regurgitation is common in infants, it may prove difficult to monitor a nursing infant for vomiting, so language conveying that only "unusual" vomiting would be a cause for concern was included in the MedGuide and patient counseling.

12.2 Postmarketing Safety Findings

As described above, hyperglycemia will be added to the post-marketing adverse events section. A new section in Warnings and Precautions was added to describe the risk of somnambulism, and information on this new warning was also added to the patient counseling section and the MedGuide; however, at this time discussions are still underway regarding whether this should be implemented in this supplement or through a separate Safety Labeling Change Letter.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action
  I recommend approval of this supplement.

- Risk Benefit Assessment

Chantix is clearly effective in helping smokers stop smoking; this effect is now confirmed in a population that expresses reluctance to quit smoking abruptly. Chantix can be used effectively according to various sets of directions, providing for treatment initiation before or after the patient sets a quit date, and now for treatment initiation followed by gradual reduction of smoking. The effect is durable, with a quit rate superior to placebo both at the end of treatment and at the end of follow-up, with patients more likely to sustain a year of abstinence if they are treated with Chantix as compared to placebo. The health benefits of a year of abstinence are well-established.

There do not appear to be new risks associated with initiating Chantix and gradually reducing smoking over three months before quitting..

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

  Chantix is currently marketed under a MedGuide-only REMS established to manage risk of neuropsychiatric events. No changes to the REMS, other than to update the MedGuide to include the new instructions, are needed.

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

/s/

CELIA J WINCHELL
06/21/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021928/S-039

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA Supplement
Application Number	021928-S039
Priority or Standard	Standard
Submit Date	October 13, 2015
Received Date	October 13, 2015
PDUFA Goal Date	August 13, 2016
Division/Office	Division of Anesthesia, Analgesia, and Addiction Products
Reviewer Name	Sarah Arnold, M.D., M.P.H.
Review Completion Date	June 8, 2016
Established Name	Varenicline tartrate
Trade Name	Chantix
Applicant	Pfizer, Inc.
Formulation	oral tablet
Dosing Regimen	New proposed regimen: 0.5 mg once daily on days 1-3, 0.5 mg twice daily on days 4-7, then 1 mg twice daily for (b) (4) weeks. During the first 12 weeks, reduce the number of cigarettes smoked to zero (reduce by 50% at week 4, further 50% by week 8, abstinent by week 12). During the second 12 weeks of treatment, subjects were expected to be abstinent from smoking.
Applicant Proposed Indication/Population	Smoking Cessation.
Recommendation on Regulatory Action	Approval
Recommended Indication/Population (if applicable)	Smoking Cessation.

Table of Contents

Table of Tables

Table of Figures

Glossary

AC	advisory committee
AE	adverse event
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity

OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

Clinical Review
Sarah Arnold, M.D., M.P.H.
NDA Supplement 039
Chantix (varenicline)

1

1 Executive Summary

1.1. Product Introduction

Chantix® (varenicline tartrate) is a first-in-class, new molecular entity (NME) approved as an aid to smoking cessation. Varenicline is a partial nicotinic receptor agonist, selective for the α4β2 nicotinic acetylcholine receptor subtype. NDA 21928 was submitted by Pfizer on (b) (4) and approved on 5/10/06.

- Trade name: Chantix®
- Drug established name: varenicline tartrate
- Chemical name: 7,8,9,10-tetrahydro-6,10-methano-6H-pyrazino[2,3-h][3]benzazepine, (2R,3R)-2,3-dihydroxybutanedioate (1:1)
- Drug class: partial α4β2 nicotinic receptor agonist
- Proposed indication: Varenicline is currently indicated for use as an aid to smoking cessation in adult smokers; the present supplement proposes to compare the efficacy and safety of varenicline to placebo for smoking cessation during the last 10 weeks of treatment, in subjects who were not willing or able to make an abrupt quit attempt, but who were willing to reduce their smoking with the ultimate goal of quitting.

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

The proposed regimen for this submission is the same 7-day titration period mentioned above for the study drug (varenicline or placebo), followed by 1 mg BID of study drug starting day 8. Subjects were to continue 1 mg BID of study drug from week 2 to week 24. Patients were asked to reduce their smoking from the baseline rate by at least 50% by week 4, with a further 50% reduction in smoking rate from week 4 to week 8, with the goal of total abstinence at week 12. Subjects could reduce their smoking rate faster

Chantix is supplied as an immediate release film-coated tablet in two strengths, 0.5 mg and 1 mg, and in blister card presentations providing appropriate combinations to initiate and continue treatment.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The results of this study demonstrate that Chantix is effective as an aid to smoking cessation in smokers who are not willing or able to make an abrupt quit attempt, but who were willing to follow a reduce-to-quit schedule with the goal of abstinence by Week 12. The pre-specified primary endpoint was exhaled carbon monoxide (CO)-confirmed 10-week continuous abstinence (CA), with the 10 weeks being counted from weeks 15-24, inclusive, using patient self-reports of cigarette and nicotine use 'since last visit' and CO measurements conducted in the clinic visit. Key secondary efficacy endpoints were the CO confirmed Continuous Abstinence Weeks 21-24 and 21-52. On both the primary and secondary efficacy endpoints, the varenicline treatment group was statistically significantly better than the placebo treatment group ($p<0.001$).

I recommend the supplement be approved with modifications to the Applicant's proposed labeling. Two new safety issues (somnambulism and glycemic disorders) have been identified by Division of Pharmacovigilance which are included in labeling modifications.

1.3. Benefit Risk Assessment

In this study population, the adverse event profile was similar to that previously established for Chantix. Common adverse events included gastrointestinal complaints (primarily nausea) and sleep disturbances (primarily abnormal dreams). Serious neuropsychiatric events were not observed more frequently in the Chantix-treated group compared to the placebo-treated group.

Chantix was clearly more effective than placebo in helping smokers achieve abstinence and maintain it to the end of the year of observation. The potential benefits of smoking cessation are substantial, and the benefit of Chantix outweighs
the risks.

2 Therapeutic Context

2.1. Analysis of Condition

Tobacco dependence is a serious and life-threatening condition due to the well-established link between smoking and cancer and a variety of cardiovascular and respiratory diseases. Many smokers make multiple attempts before quitting successfully, and relapse even after a successful quit attempt is common.

Although many smokers are interested in quitting, some are reluctant to quit completely and the idea of quitting by gradual reduction (known as "reduce-to-quit" (RTQ) or "cut down-to-quit" in literature) is considered an attractive option. Notably, there has been some doubt whether such a regimen would be effective. Behavioral methods involving gradual reduction of smoking ("fading") have not generally been regarded as effective (Lindson-Hawley, 2016). Furthermore, it is also believed that any smoking at all after the "quit date" is associated with a greatly reduced chance of successful abstinence, as evidenced by the similarity in responder rates when previous trials of nicotine replacement therapy (NRT) have been analyzed with respect to "abstinence" vs. "abstinence, slip allowed." It is theorized that as the number of cigarettes per day is reduced, each remaining cigarette smoked is more reinforcing, making the behavioral change more difficult. Because Chantix is thought to make smoking less reinforcing, it may be helpful in facilitating a gradual reduction approach to smoking cessation that may be more appealing to reluctant quitters.

2.2. Analysis of Current Treatment Options

Chantix® (varenicline tartrate) is a first-in-class, new molecular entity (NME) approved as an aid to smoking cessation. Varenicline is a partial nicotinic receptor agonist, selective for the α4β2 nicotinic acetylcholine receptor subtype. NDA 21928 was submitted by Pfizer on 11/11/05 and approved on 5/10/06.

- Trade name: Chantix®
- Drug established name: varenicline tartrate
- Chemical name: 7,8,9,10-tetrahydro-6,10-methano-6H-pyrazino[2,3-h][3]benzazepine, (2R,3R)-2,3-dihydroxybutanedioate (1:1)
- Drug class: partial α4β2 nicotinic receptor agonist
- Proposed indication: Varenicline is currently indicated for use as an aid to smoking cessation in adult smokers; the present supplement proposes to compare the efficacy and safety of varenicline to placebo for smoking cessation during the last 10 weeks of treatment, in subjects who were not willing or able to make an abrupt quit attempt, but who were willing to reduce their smoking with the ultimate goal of quitting. Dose: 1 mg by mouth twice daily
    - 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
- The proposed regimen for this submission is the same 7-day titration period mentioned above for the study drug (varenicline or placebo), followed by 1 mg BID of study drug starting day 8. Subjects were to continue 1 mg BID of study drug from week 2 to week 24. Patients were asked to reduce their smoking from the baseline rate by at least 50%

by week 4, with a further 50% reduction in smoking rate from week 4 to week 8, with the goal of total abstinence at week 12. Subjects could reduce their smoking rate faster

Chantix is supplied as an immediate release film-coated tablet in two strengths, 0.5 mg and 1 mg, and in blister card presentations providing appropriate combinations to initiate and continue treatment.

Table 1. Summary of Treatment Options for Smoking Cessation

DRUGS USED AS AIDS TO SMOKING CESSATION			
Generic/Chemical Name	**Trade Name**	**Sponsor(s)**	**Dosage form(s)**
Nicotine polacrilex	Nicorette gum, chewing (OTC; also generic)	GlaxoSmithKline Consumer Healthcare LP	• Chewing pieces (transmucosal)
Nicotine polacrilex	Nicorette (F/K/A Commit) Lozenge (OTC; also generic) Nicorette Mini-Lozenge	GlaxoSmithKline Consumer Healthcare LP	• Lozenges – buccal delivery system
Nicotine patch	Habitrol (also generic)	Dr. Reddy	• Transdermal • Film, extended release
Nicotine patch	Nicoderm CQ (also generic)*	Sanofi Aventis/Glaxo Smith Kline Consumer Healthcare LP	• Transdermal • Film, extended release
Nicotine oral inhaler	Nicotrol	Pfizer/Pharmacia and Upjohn	• Cartridge with mouthpieces – buccal delivery system
Nicotine nasal spray	Nicotrol	Pfizer/Pharmacia and Upjohn	• Solution with metered spray pump
Bupropion	Zyban	GlaxoSmithKline	• Oral tablets

*Other NDA transdermal products including Nicotrol TD, and ProStep are no longer marketed.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Varenicline is currently marketed in the United States only in Chantix tablets. The applicant, Pfizer, holds patents on several steps in the varenicline manufacturing process. No other domestic varenicline sources are known. No other α4β2 nicotinic agonist medications have been approved for use in the United States or elsewhere. At least one structurally and pharmacologically similar drug, (b) (4)

(b) (4)

3.2. Summary of Presubmission/Submission Regulatory Activity

Pfizer submitted a type C Meeting request regarding protocol details for this submission in April, 2010. The Division sent an advice letter addressing questions addressed on grace period, secondary endpoints, and labeling in lieu of meetings. Pfizer sent a draft protocol for review in November, 2010. The Division reviewed the protocol and advised Pfizer to include subjects with mild to moderate depression and anxiety disorders stabilized on medication, otherwise, the Division had no other issues with the protocol. In addition, the Agency has recently reviewed the following issues:

1. Potentiation of alcohol's effects by Chantix

In October 2013, Pfizer submitted a supplement (S-32) (b) (4) a Safety Labeling Change letter was sent to Pfizer on 8/6/14, requesting the addition of a warning about the potentiation of alcohol's intoxicating effects by Chantix. Section 5.3 of the label, "Interactions with Alcohol," was added 9/14.

2. Seizures associated with Chantix

An OSE review of post-marketing cases of seizures concluded that a new warning should be added to labeling. This was also included in the SLC letter of 8/6/14. (b) (4) Section 5.2 of the label, "Seizures," was added 9/14.

3. Revisions to labeling regarding neuropsychiatric adverse events

A supplement to add information on neuropsychiatric adverse effects, from pooled analyses of clinical trials and from observational studies, was submitted on 4/8/14. Changes to labeling were discussed at an Advisory Committee Meeting on October 16, 2014. Section 5.1 of the label, "Neuropsychiatric Symptoms and Suicidality," was added 9/14, and a boxed warning remains in the label following the Advisory Committee's recommendations. (b) (4)

3.3. Foreign Regulatory Actions and Marketing History

No new foreign regulatory actions have been reported since the last supplement was approved.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

In consultation with the Office of Scientific Investigations, it was determined that routine inspections would not be requested because there have been several recent similar studies by the Sponsor which have been inspected with no remarkable findings.

4.2. Product Quality

No new information.

4.3. Clinical Microbiology

N/A

4.4. Nonclinical Pharmacology/Toxicology

No new information.

4.5. Clinical Pharmacology

No new information was submitted. The following summary of clinical pharmacology is from the package insert.

4.5.1. 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.

4.5.2. Pharmacodynamics

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.

4.5.3. **Pharmacokinetics**

This section should describe the known human PK characteristics, including exposure (e.g., Cmax, Cmin, area under the curve), half-life, dose proportionality, absorption, distribution, metabolism, and excretion. *In vitro* and *in vivo* data on drug-drug interactions should also be discussed. There should be an assessment of whether the drug will be an important inhibitor or inducer of the metabolism or transport of other drugs, and whether it will be affected by inhibitors or inducers. You should also describe the PK effects of drug-demographic and drug-disease interactions (e.g., renal impairment, hepatic impairment). For orally administered products, summarize whether bioavailability is affected by food. Summary tables are particularly useful in this section. Where there are genetic factors that can affect PK importantly (e.g., CYP450, (b) (4)), these should be noted.
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. Additionally, in subjects with ESRD, varenicline was efficiently removed by hemodialysis.

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) are unlikely to be affected by varenicline.

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.

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.

4.6. Devices and Companion Diagnostic Issues

N/A

4.7. Consumer Study Reviews

N/A

5 Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The efficacy data derives from a single study, Study A3051075. The tables below (from Pfizer's Integrated Summary of Safety) show the studies included in the pooled safety data.

Table 2. Description of Studies: Varenicline Placebo-Controlled Phase 2-4 Studies Completed as of 31 December 2014

Study	Design	Duration	Treatment Groups	No. of Subjects
PHASE 2				
A3051002 Dose-ranging	R, PB, DB, PC and active-control	Varenicline: 6 weeks treatment plus 1 week placebo; Zyban: 7 weeks treatment nontreatment follow-up to Week 52	Varenicline 0.3 mg QD Varenicline 1 mg QD Varenicline 1 mg BID Zyban 150 mg BID Placebo	126 126 125 126 123 Total: 626
A3051007 titration (nontreatment follow-up in Study **A3051018**)	R, PG, DB, PC	12 weeks treatment, plus nontreatment follow-up to Week 52	Varenicline 0.5 mg NT Varenicline 0.5 mg T Varenicline 1 mg NT Varenicline 1 mg T Placebo	124 129 124 129 121 Total: 627
A3051016 Flexible dosing (nontreatment follow-up in Study **A3051019**)	R, PG, DB, PC	12 weeks treatment, plus nontreatment follow-up to Week 52	Varenicline flexible dosing 0.5 to 2 mg daily Placebo	157 155 Total: 312
A3051046_48[b] Japan	R, PG, DB, PC	12 weeks treatment, plus nontreatment follow-up to Week 52	Varenicline 0.25 mg BID Varenicline 0.5 mg BID Varenicline 1 mg BID Placebo	153 155 156 154 Total: 618
PHASE 3 STUDIES				
A3051028 Zyban comparison (pivotal study)	R, PG, DB, PC and active comparator	12 weeks treatment, plus nontreatment follow-up to Week 52	Varenicline, 1 mg BID Zyban 150 mg BID Placebo	349 329 344 Total: 1022
A3051036 Zyban comparison (pivotal study)	R, PG, DB, PC and active comparator	12 weeks treatment, plus nontreatment follow-up to Week 52	Varenicline, 1 mg BID Zyban 150 mg BID Placebo	343 340 340 Total: 1023
A3051037 Long-term safety	R, PG, DB, PC	52 weeks treatment	Varenicline, 1 mg BID Placebo	251 126 Total: 377
A3051045 Taiwan and Korea	R, PG, DB, PC	12 weeks treatment, plus nontreatment follow-up to Week 24	Varenicline, 1 mg BID: Placebo	126 124 Total: 250
A3051049 CV disease	R, PG, DB, PC	12 weeks treatment, plus nontreatment follow-up to Week 52	Varenicline, 1 mg BID: Placebo	353 350 Total: 703

A3051054 COPD	R, PG, DB, PC	12 weeks treatment, plus nontreatment follow-up to Week 52	Varenicline, 1 mg BID: Placebo	248 251 Total: 499
A3051055 Multinational Asian sites	R, PG, DB, PC	12 weeks treatment, plus nontreatment follow-up to Week 24	Varenicline, 1 mg BID: Placebo	165 168 Total: 333
A3051072 Schizophrenia/ Schizoaffective disorder	R, PG, DB, PC	12 weeks treatment, plus nontreatment follow-up to Week 24	Varenicline, 1 mg BID: Placebo	84 43 Total: 127

Study	Design	Duration	Treatment Groups	No. of Subjects[a]
PHASE 4 STUDIES				
A3051075[c] Reduce-to-quit	R, PG, DB, PC	24 weeks treatment, plus nontreatment follow-up to Week 52	Varenicline, 1 mg BID: Placebo	751 742 Total: 1,493
A3051080 Multinational sites in Africa, Mid-East, S. America	R, PG, DB, PC	12 weeks treatment, plus nontreatment follow-up to Week 24	Varenicline, 1 mg BID: Placebo	390 198 Total: 588
A3051095 Flexible quit date	R, PG, DB, PC	12 weeks treatment, plus nontreatment follow-up to Week 24	Varenicline, 1 mg BID: Placebo	486 165 Total: 651
A3051104 Smokeless tobacco	R, PG, DB, PC	12 weeks treatment, plus nontreatment follow-up to Week 26	Varenicline, 1 mg BID: Placebo	213 218 Total: 431
A3051115 Assessment of neuropsychiatric symptoms in quitting smokers	R, PG, DB, PC	12 weeks treatment, plus 30 day nontreatment follow-up	Varenicline, 1 mg BID: Placebo	55 55 Total: 110
A3051122 Depression	R, PG, DB, PC	12 weeks treatment, plus nontreatment follow-up to Week 52	Varenicline, 1 mg BID: Placebo	256 269 Total: 525
A3051139 Re-treatment	R, PG, DB, PC	12 weeks treatment, plus nontreatment follow-up to Week 52	Varenicline, 1 mg BID: Placebo	249 245 Total: 494

a. No. of Subjects = subjects randomized and treated by treatment group and in total.
b. A3051048 was an extension of A3051046.
c. Study included in 19-Study Cohort and analyzed as a cohort of its own.
Note: All studies enrolled smokers with the exception of A3051104 which enrolled smokeless tobacco users.
DB=Double-blind; PC=placebo-controlled; PG=parallel group; R=randomized; QD=once daily; BID=twice daily; NT=Not Titrated; T=Titrated; COPD=chronic obstructive pulmonary disease; S.=South; CSR=Clinical Study Report.
Source: A3051002 CSR, A3051007 CSR, A3051016 CSR, A3051028 CSR, A3051036 CSR, A3051037 CSR, A3051045 CSR, A3051046_48 CSR, A3051049 CSR, A3051054 CSR, A3051055 CSR, A3051072 CSR, A3051075 CSR, A3051080 CSR, A3051095 CSR, A3051104 CSR, A3051115 CSR, A3051122 CSR, A3051139 CSR.

Table 3. Supplement 039 Smoking Cessation Through Reduction

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety							
A3011075	Randomized Double-Blind Placebo Controlled	Varenicline 1 mg bid for 12 weeks starting with a 1-week titration, with an optional additional 12 weeks to maintain abstinence	Primary: Continuous Abstinence Rate (CAR), weeks 15-24 Secondary: CAR weeks 21-24 and 21-52	52 weeks	1510 760 Varenicline 750 Placebo	Adults (≥18yrs) cigarettes smokers not willing or able to make an abrupt quit attempt, but were willing to reduce their smoking with the ultimate goal of quitting.	61 Centers, 10 Countries: Australia (4) Canada (6) Germany (6) Czech Republic (6) UK (7) Egypt (3) Japan (6) Mexico (4) Taiwan (7) US (12)

5.2. Review Strategy

The single clinical trial was reviewed individually for efficacy. The safety review was based on the single clinical trial as well as an Integrated Summary of Safety.

The following sections are non-applicable to this review because no significant issues from other review disciplines pertinent to clinical conclusions of efficacy and safety were submitted, or the section is not relevant to this product:

- 4.2 Product Quality
- 4.3 Clinical Microbiology
- 4.4 Nonclinical Pharmacology/Toxicology
- 4.5 Clinical Pharmacology
- 4.6 Devices and Companion Diagnostic Issues
- 4.7 Consumer Study Reviews
- 7. Integrated Review of Effectiveness
- 9. Advisory Committee Meeting

The protocol, conduct, and demographic results of trial A3051075 are reviewed in sub-section 6.1.2. and the efficacy data for trial A3051075 will be reviewed in section 6. The safety data from trial A3051075 and the integrated safety data from all relevant studies are reviewed in section 8. See Section 8 for a listing of deleted sections of the Safety Review.

6 Review of Relevant Individual Trials Used to Support Efficacy

6.1. Protocol A3051075: A Phase 4, Multi-National, Randomized, Double-Blind, Placebo Controlled Study to Evaluate the Efficacy and Safety of Varenicline Compared to Placebo for Smoking Cessation Through Reduction, Conducted July 19, 2011- July 12, 2013

6.1.1. Study Design

Overview and Objective

According to the Sponsor, many smokers express a desire to quit by gradually reducing the number of cigarettes smoked until they stop completely ('Reduce to Quit'). Previous efforts to establish effective regimens of quitting by gradual reduction using nicotine replacement therapy have yielded discouraging results. The primary objective of trial A3051075 is to compare the efficacy of varenicline to placebo for smoking cessation during the last 10 weeks of treatment in subjects who are not willing or able to make an abrupt quit attempt but are willing to reduce their smoking with the ultimate goal of quitting. Secondary objectives are the comparison of varenicline to placebo during the last four weeks of treatment and through the longer-term follow-up phase to Week 52.

Trial Design

This trial is a Phase 4, randomized, double-blind, placebo-controlled, parallel group, multicenter study designed to evaluate the efficacy and safety of varenicline in subjects who are not able to make an abrupt quit attempt but are willing to reduce their smoking with the ultimate goal of quitting.

Population and Procedures

Inclusion/Exclusion Criteria

Planned enrollment was approximately 1404 subjects at approximately 75 sites; 702 subjects per arm.

To be eligible, subjects were required to meet the following criteria:

- Cigarette smokers over the age of 18 years who are not willing/able to quit smoking within the next month but who are willing to attempt to reduce their smoking to work toward a quit attempt within the next 3 months.
- Subjects must have smoked an average of at least 10 cigarettes per day during the past year and during the month prior to the screening visit, with no continuous period of

abstinence greater than 3 months in the past year and who have an exhaled carbon monoxide (CO) >10 ppm at screening.

- Subjects with history of lifetime or current mild to moderate (investigator opinion) major depressive disorder (MDD), depression, depressed mood, anxiety, and anxiety disorders (including general anxiety disorder (GAD), obsessive compulsive disorder (OCD) and phobias such as agoraphobia and social phobia) could be included if their condition was stable. Stability is defined as:
    - If on medication, on the same dose for the past 6 months; No hospitalizations for exacerbations in the past 6 months.
- Females who are of childbearing potential could be included provided that they are not pregnant, not nursing, and use an acceptable means of contraception (oral contraceptive agent, intrauterine device (IUD), implantable contraception (e.g., Norplant), an injectable contraceptive (e.g., Depo Provera), or double barrier method of contraception, (i.e., condom plus spermicide in combination with a female condom, diaphragm, cervical cap, or IUD), or sexual abstinence, for at least 1 month prior to entering the study and will continue its use through at least 30 days after the last dose of study medication.

Subjects were to be excluded for:

- Pregnancy or nursing.
- A history of a suicide attempt or any suicidal behavior in the past two years as assessed using the C-SSRS and/or the SBQ- R.
- History of suicidal ideation with intent/plan in the past 6 months ("yes" to Questions 4 and/or 5 on the C-SSRS) or at the screening or baseline visit.
- A lifetime or current severe major depressive disorder (MDD), depression, depressed mood, anxiety, or anxiety disorder (including generalized anxiety disorder (GAD), obsessive-compulsive disorder (OCD), and phobias such as agoraphobia and social phobia).
- Unstable mild to moderate major depressive disorder (MDD), depression, depressed mood, anxiety, or anxiety disorder (including generalized anxiety disorder (GAD), obsessive-compulsive disorder (OCD), and phobias) such as agoraphobia and social phobia.
- A lifetime diagnosis or treatment for psychosis, panic disorder, bipolar disorder, post-traumatic stress disorder (PTSD), or schizophrenia.
- Alcohol or substance abuse or dependence (except nicotine) unless in full remission for at least 12 months.
- A positive urine drug screen (at screening or baseline) for drugs of abuse/potential abuse not prescribed for the treatment of a medical condition.
- Previous participation in a varenicline study, or previously taken Chantix®/ Champix®.
- SGOT (AST) or SGPT (ALT) greater than 3 times the upper limit of normal (ULN) or total bilirubin greater than 2 times the ULN at screening.

- Clinically significant medical disorders or clinically significant laboratory test abnormalities as determined by the Principal Investigator.
- Severe chronic obstructive pulmonary disease (COPD) defined as any subject who fulfills any of the following criteria:
    - History of repeated exacerbations of COPD (greater than or equal to 3 in 3 years).
    - Requires systemic corticosteroid maintenance (e.g., oral prednisolone) for management of chronic symptoms.
    - Is maintained on oxygen therapy for management of chronic symptoms.
- A recent (<5 years) history of cancer. Subjects with completely excised carcinoma in situ of the cervix or completely excised melanomas <5 years prior to screening may be considered pending discussion with the study clinician. Subjects with a remote (>5 years) history of cancer may be considered pending discussion with the study clinician. Cured basal cell or squamous cell carcinoma of the skin are allowed.
- Evidence or history of clinically significant allergic reactions to drugs (e.g., anaphylaxis or Stevens-Johnson syndrome).
- A clinically significant ECG at the screening visit (as determined by the Principal Investigator or medically appropriate designee).
- Clinically significant cardiovascular disease in the past 2 months. Examples of clinically significant cardiovascular disease include:
    - Myocardial infarction;
    - Coronary artery bypass graft (CABG);
    - Percutaneous transluminal coronary angioplasty (PTCA);
    - Severe or unstable angina;
    - Serious arrhythmia;
    - Clinically significant ECG conduction abnormalities;
    - Heart failure.
- Clinically significant cerebrovascular disease in the past 2 months. Examples of clinically significant cerebrovascular disease include:
    - Cerebrovascular accident (CVA), stroke;
    - Documented transient ischemic attack (TIA).
- Unwillingness to abstain from using non-cigarette tobacco products (including pipe tobacco, cigars, snuff, chewing tobacco, etc.) or marijuana during study participation.
- Unwillingness to abstain from using nicotine replacement therapy and other aids to smoking cessation during the treatment period.
- Intention to donate blood or blood components while receiving study drug or within 1 month of the completion of the treatment phase of the study.
- Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate

for entry into this study.

- Disallowed concomitant medications included:
  - Any investigational drug unconnected with the study
  - Nicotine replacement therapy and other aids to smoking cessation, including herbal medications (during treatment phase).
  - Bupropion;
  - Naltrexone;
  - Chronic use of oral and injectable steroids;
  - Insulin;
  - Clonidine:
  - Nortryptiline;
  - Warfarin;
  - Theophylline;
  - Herbal medications used in the treatment of anxiety disorders
  - Over the counter and prescribed stimulants and anorectic agents.

Procedures

The protocol called for an initial screening period of 3-10 days, during which medical screening procedures were undertaken. A subsequent baseline visit was to occur after review of laboratory tests and EKG confirmed eligibility. Only subjects continuing to meet enrollment criteria at the baseline visit were to be randomized on a 1:1 ratio to varenicline 1 mg BID or matching placebo for a 24 week double-blind treatment phase divided into two 12 week periods; a 12 week reduction phase, and a 12 week abstinence phase.

12 Week Reduction Phase: During this double-blind treatment phase, subjects were to attend the clinic for visits at Weeks 1, 2, 4, 6, 8, and 12. Telephone visits were conducted at Weeks 3, 5, 7, and 10. There were no visit assessments scheduled for Weeks 9 and 11. Efficacy and safety evaluations were to be undertaken at the clinic visits, and brief smoking cessation counseling (less than 10 minutes) provided at all visits from baseline through to Week 12. Site personnel were to dispense study drug (varenicline 1 mg BID or placebo) at clinic visits only.

12 Week Abstinence Phase: The same randomization assignments continued into this additional 12-week phase. During this abstinence phase, the subjects were to come to the clinic for visits at Weeks 15, 18 and 21-24. Site personnel were to conduct telephone visits at Weeks 14 16, and 20. There were no visit assessments scheduled for Weeks 13, 17 and 19. Site personnel were to dispense study medication at clinic visits in sufficient quantity to last until the next clinic visit. Subjects were expected to begin abstinence at Week 12 and were encouraged to remain abstinent for the duration of the protocol. If a subject did not make a quit attempt in the reduction phase he/she would be encouraged to do so in this phase.

28 Week Post Treatment Follow-up Phase (Follow-Up to Week 52): Study drug was planned to be discontinued at Week 24 and subjects would continue into the post -treatment follow-up phase. Clinic visits would take place at Weeks 26, 32, 40, 48 and 52. Telephone contact was planned for Weeks 28, 36 and 44.

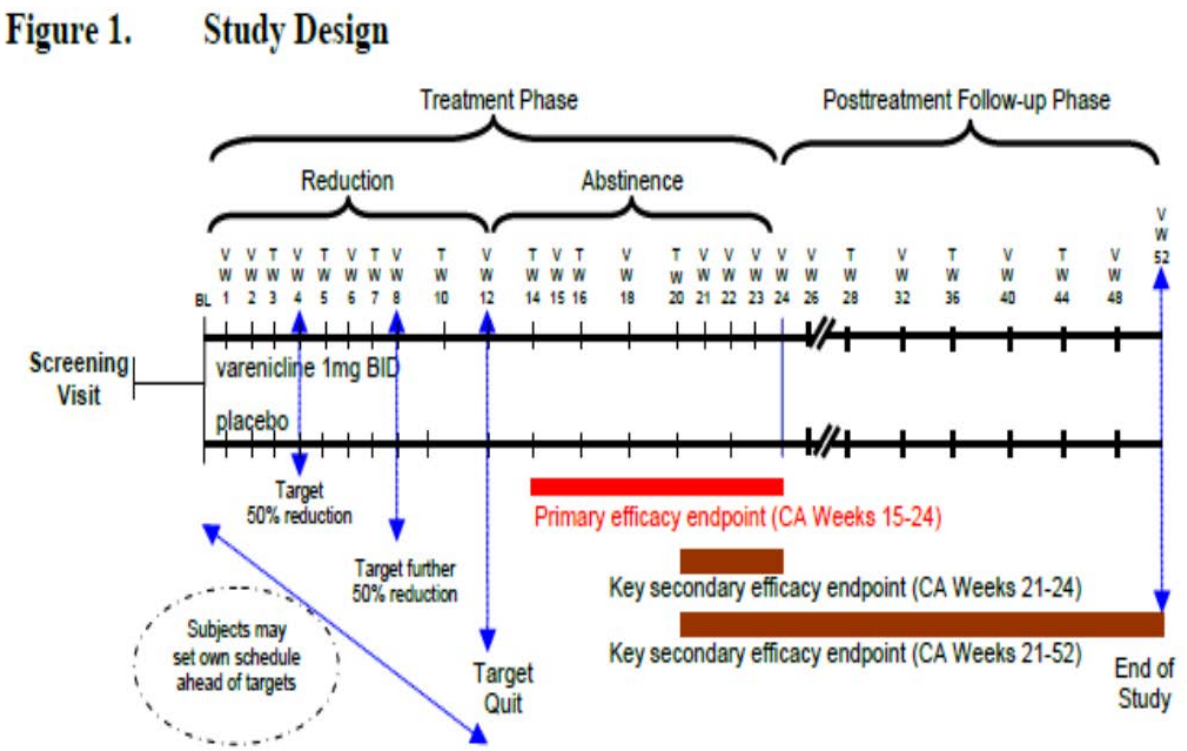
Dosing

Study drug titration to the full dose during the first week was to occur in the following manner:

- varenicline 0.5 mg or matching placebo QD for 3 days,
- varenicline 0.5 mg or matching placebo BID for 4 days,
- then varenicline 1 mg or matching placebo BID for the following 23 weeks.

Subjects who had difficulties with tolerability could have the blinded dose lowered temporarily or permanently to 0.5 mg BID. Dosing was to continue until the completion of the treatment phase at the Week 24 visit. The figure below, from Pfizer's submission, illustrates the study design and schedule.

Figure 1. Schedule of Visits and Assessments



BL = Baseline; CA = continuous abstinence; T = telephone contact; V = clinic visit; W = week

Source: Protocol (Appendix 16.1.1).
Note: All subjects randomized to receive varenicline were titrated to the full dose during the first week in the following manner: 0.5 mg once daily (QD) for 3 days, 0.5 mg BID for 4 days, then 1 mg BID for the following 23 weeks.

Behavioral Treatment

Smoking cessation counseling, in accordance with Agency for Healthcare Research and Quality (AHRQ) guidelines and/or suggested reduction techniques, were to be given at each visit during the reduction phase, the abstinence phase, and the posttreatment follow up phase. The counseling was to be 1:1 and up to 10 min in duration and would be tailored to the subject's needs at that point in time. Whenever possible, counseling would be conducted by the same counselor throughout, so that the relationship could build and bring additional value to the sessions.

The following Time-and-Events tables from Pfizer's submission illustrate the planned schedule of assessments.

Table 4. Schedule of Activities: Screening Visit to Week 12

Protocol Activity	Screening	Baseline	Week 1	Week 2	Week 3 Telephone Visit	Week 4	Week 5 Telephone Visit	Week 6	Week 7 Telephone Visit	Week 8	Week 10 Telephone Visit	Week 12
	Screening Phase	Treatment Phase										
Window			+/-3 days	+/-3 days	+/-3 days	+/-3 days	+/-3 days	+/-3 days	+/-3 days	+/-3 days	+/-3 days	+/-3 days
Page 1 of 2												
Informed consent	X											
Medical history	X											
Physical examination	X	X										
Vital signs and weight	X	X										X
Height	X											
Hematology	X											
Blood chemistry	X											
Pregnancy test[a]	X	X										X
Urine drug screen[b]	X	X										
12-Lead ECG[c]	X											
Registration/Randomization		X										
Sample banking of exploratory research[d]	X											
Smoking history	X											
Tobacco Dependence Screener (TDS)	X											
Fagerström test	X											
Exhaled carbon monoxide (CO)	X	X	X	X		X		X		X		X
Nicotine Use Inventory (NUI)		X	X	X	X	X	X	X	X	X	X	X
Concomitant medications and concomitant non-drug treatments	X	X	X	X		X		X		X		X
Concomitant drugs (for smoking cessation)	X	X	X	X		X		X		X		X
Dispense investigational product		X	X	X		X		X		X		X
Dosing record			X	X		X		X		X		X

Table 5. Schedule of Activities: Week 14 to Week 24

Protocol Activity	Week 14 Telephone Visit	Week 15	Week 16 Telephone Visit	Week 18	Week 20 Telephone Visit	Week 21	Week 22	Week 23	Week 24
	Treatment Phase								
Window			+/-3 days	+/-3 days	+/-3 days	+/-3 days	+/-3 days	+/-3 days	+/-3 days
Physical examination									X
Vital signs and weight									X
Pregnancy test[a]									X
Exhaled carbon monoxide (CO)		X		X		X	X	X	X
Nicotine Use Inventory (NUI)	X	X	X	X	X	X	X	X	X
Concomitant medications and concomitant non-drug treatments		X		X		X	X	X	X
Concomitant drugs (for smoking cessation)		X		X		X	X	X	X
Dispense investigational product		X		X		X	X	X	
Dosing record		X		X		X	X	X	X
Adverse events		X		X		X	X	X	X
NAEI		X		X		X	X	X	X
C-SSRS		X		X		X	X	X	X
PHQ-9	X		X	X	X		X		X
mCEQ[b]		X		X					X
MNWS		X		X					X
Smoking cessation counseling (up to 10 minutes)	X	X	X	X	X	X	X	X	X

Source: Protocol (Appendix 16.1.1).
C-SSRS = Columbia-Suicide Severity Rating Scale; mCEQ = Modified Cigarette Evaluation Questionnaire; MNWS = Minnesota Nicotine Withdrawal Scale; NAEI = Neuropsychiatric Adverse Event Interview; PHQ-9 = Patient Health Questionnaire-9.
[a] Dipstick at site
[b] Administered to only those subjects who smoked since the visit or since the last time they completed the form

Table 6. Schedule of Activities: Week ET24 to Week ET52

Protocol Activity	Week ET_{24}	Week 26	Week 28 Telephone Visit	Week 32	Week 36 Telephone Visit	Week 40	Week 44 Telephone Visit	Week 48	Week 52	Week ET_{52}
	Treatment Phase	Posttreatment Follow-Up Phase								
Window		+/-7 days	+/-3 days	+/-7 days	+/-3 days	+/-7 days	+/-3 days	+/-7 days	+/-7 days	
Physical examination	X									
Vital signs and weight	X									
Pregnancy Test[a]	X									
Exhaled carbon monoxide (CO)	X	X		X		X		X	X	X
Nicotine Use Inventory (NUI)	X	X	X	X	X	X	X	X	X	X
Concomitant medications and concomitant non-drug treatments	X	X		X		X		X	X	X
Concomitant drugs (for smoking cessation)	X	X		X		X		X	X	X
Dosing record	X									
Adverse events	X	X		X		X		X	X	X
NAEI	X	X		X		X		X	X	X
C-SSRS	X	X		X		X		X	X	X
PHQ-9	X	X		X		X		X	X	X
mCEQ[b]	X	X								
MNWS	X	X								
Smoking cessation counseling (up to 10 minutes)		X	X	X	X	X	X	X	X	X

Source: Protocol (Appendix 16.1.1).
C-SSRS = Columbia-Suicide Severity Rating Scale; ET = early termination; mCEQ = Modified Cigarette Evaluation Questionnaire; MNWS = Minnesota Nicotine Withdrawal Scale; NAEI = Neuropsychiatric Adverse Event Interview; PHQ-9 = Patient Health Questionnaire-9.
[a] Dipstick at site
[b] Administered to only those subjects who smoked since the last visit or since the last time they completed the form

The pre-specified primary endpoint was exhaled carbon monoxide (CO)-confirmed 10-week continuous abstinence (CA), with the 10 weeks being counted from weeks 15-24, inclusive, using patient self-reports of cigarette and nicotine use 'since last visit' and CO measurements conducted in the clinic visit. This aligns with previous endpoints which allowed two weeks of "grace" from the scheduled Quit Day (end of Week 12) and continued through the end of dosing. Subjects were to be classified as responders if they were able to maintain complete abstinence from cigarette smoking and other nicotine use for the last 10 weeks of treatment with end-expiratory exhaled CO measurements ≤ 10 ppm.

Continuous abstinence from weeks 15-24 was defined as being abstinent from smoking and the use of any other nicotine products at the week 15 visit through the week 24 visit as determined by direct questioning and supported by CO monitoring. Continuous abstinence at a timepoint from week 21 or later was defined as remaining abstinent as determined at the week 21 visit and each weekly visit through the week 24 visit (the last 4 weeks of the treatment phase), and then through the time points being summarized. Response for continuous abstinence was determined by evaluating each subject's smoking status and use of nicotine products (at weeks 15-24) or tobacco products (weeks 26-52) based on the 'since last contact' question in the NUI.

In the case of a missed visit or visits during the evaluation period of weeks 15-24, a subject was considered a responder if the subject met the following criterion: The subject responded that they had NOT smoked or used nicotine products 'since the last visit' at the visit after the missing visit or visits. In the Sponsor's analysis, missing CO measurements were imputed as negative (< 10 ppm), therefore not disqualifying the subject as a responder.

Smoking status was determined from patient self-reports of smoking and the use of nicotine products 'since the last study visit' questions using the NUI. No attempt was made to impute missing data from other interview questions. Subjects who discontinue study drug treatment were not discontinued from the study, and were to be encouraged to maintain the visit schedule and continue participation through the post treatment follow-up phase of the study.

Key secondary efficacy endpoints were the CO confirmed Continuous Abstinence Weeks 21-24 and 21-52, and other secondary endpoints were the 7-day "point prevalence" of smoking cessation at Weeks 12, 24, and 52, and the 4-week point prevalence of smoking cessation at Week 52.

Statistical Analysis Plan

The protocol specified that the primary efficacy analysis population would be all randomized subjects. To support the robustness of the conclusions made on the "All Randomized" population, the primary endpoint and key secondary endpoint analyses would also be performed in the "Completer subjects" population (subset of the all randomized population who have at least 80% treatment compliance as measured by having any dose of study medication for at least 80% of the planned number of days in the trial treatment period).

The statistical analysis plan stipulated that logistic regression models would be used in the analyses of primary and key secondary endpoints, including treatment and center as independent variables. Treatment by center interaction was to be investigated; however, the reported p-values will be based on the main effects model.

In order to preserve the type I family-wise error rate of 0.05, a step-down procedure was planned for the analysis of the primary and the key secondary endpoints. The hierarchy of comparisons were specified:

1. CA for Weeks 15 through 24.

2. 4-week CA for Weeks 21 through 24.

3. CA for Weeks 21 through 52.

Statistical tests were to be two-sided with a 0.05 level of significance. No adjustments for the analysis of multiple secondary endpoints was planned.

A detailed evaluation of the Applicant's planned statistical analysis is in the statistical review.

Protocol Amendments

Protocol Amendments taking effect after enrollment began were administrative in nature, and did not influence the study results. The protocol was reviewed and compared to the study report to ensure all amendments were incorporated. Neither changes in study endpoints, general safety measurements, nor changes in interim assessments were reported. The Neuropsychiatric Adverse Event Inventory (NAEI), which was being developed for use in the post-marketing study focused on characterizing the rate of neuropsychiatric adverse events associated with Chantix, bupropion, and transdermal nicotine, was also used in this study. A change to wording of one of the items was made during the conduct of the study, but the NAEI is not used as an outcome measure in this study. Changes in the analysis plan are noted below.

Changes in the Planned Analyses

The original Final SAP (Version 1.2, dated 08 June 2011), and the SAP addenda (07 December 2011 and 12 November 2012) are provided in Appendix 16.1.9.

SAP Addendum (dated 07 December 2011)
This addendum added Weeks 15, 21, and 23 in Appendix 1 of the SAP, to comply with the visit schedule in the protocol for unplanned visits.

SAP Addendum (dated 12 Nov 2012)
An SAP addendum (dated 12 Nov 2012) provided details of team decisions on how to handle "3-tier AE reporting." The decisions stated in the addendum reflect the Guide Document for the 3-Tier Adverse Event Reporting for Individual Varenicline (A305) Clinical Trials (14 May 2012).

Data Quality and Integrity: Sponsor's Assurance

Pfizer provided the following information about study monitoring: To ensure consistent collection of data, all study sites were initiated during a sponsor investigator meeting or a site visit by the sponsor or designated representative.

During study conduct, the sponsor or its agent conducted regular monitoring visits to ensure that the protocol and GCP were being followed. The monitors reviewed source documents to confirm that the data recorded on CRFs were accurate. The investigator and institution allowed the sponsor's monitors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification.

Routine investigator site audits were performed by Pfizer Medical Quality Assurance at 5 sites: center 1053 (Japan; 04 to 07 September 2012), center 1044 (USA; 10 to 12 April 2012), center 1069 (Australia; 01 to 03 August 2012), center 1033 (Canada; 10 to 12 April 2012), and center 1020 (Czech Republic; 07 to 09 January 2013). These audits were conducted according to the sponsor's procedures and GCP guidelines.

Compliance with Good Clinical Practices

This study was designed and monitored in accordance with the Sponsor's standard operating procedures, which comply with the ethical principles of Good Clinical Practice (GCP) (International Conference on Harmonization 1996) as required by the major regulatory authorities, and in accordance with the Declaration of Helsinki (World Medical Association 2008) and the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002).

Financial Disclosure

A Form FDA 3455, Disclosure Statement, was provided for each clinical investigator who, or whose spouse or dependent child, had disclosable financial interests in and/ or arrangements with any sponsor of the covered clinical study. Five of the 215 clinical investigators listed in the study report had financial information to disclose, receiving payments exceeding the threshold amount of $24,999.00, which represents 2.33% of the total number of all clinical investigators who participated in the study. These include: (b) (6), site (b) (6)) $180,000, (b) (6), site (b) (6) $109,256.69, (b) (6) site (b) (6) - $102,000, (b) (6), site (b) (6))- $28,391, and (b) (6) site (b) (6)), $33,628.50. See efficacy summary at the end of this section for efficacy analysis excluding sites (b) (6) .

Subject Disposition

A total of 1510 subjects were randomized into the study and comprise the All Randomized (ITT) population. Of these subjects, 9 assigned to the varenicline group and 7 assigned to the placebo group were withdrawn from the study before the start of the treatment period. One additional subject (Subject (b) (6)) in the placebo group was withdrawn from treatment before the start of the treatment period but remained in the study. A total of 1493 subjects took at least 1 dose of study drug and comprise the All Treated population. Overall, the rates of completion of the study were higher in the varenicline treatment group than in the placebo treatment group (73.6% vs 68.7%, respectively, for the All Randomized population).

Discontinuations from the overall study were lower in the varenicline group than in the placebo group (25.6% vs 30.6%, respectively, for the All Treated population). The most common reasons for discontinuation from the overall study in the All Treated population were (1) loss to follow-up (10.1% of varenicline treatment group and 10.9% of placebo treatment group) and (2) no longer willing to participate (7.2% of varenicline treatment group and 8.0% of placebo treatment group). Review of the Case Report Form (CRF) comments confirmed that these categories did not mask other discontinuations due to adverse events. Discontinuations from

treatment were also lower in the varenicline group than in the placebo group (28.1% vs 33.7%), with a notable difference in the between-group frequency of reasons for discontinuation in the All Treated population only observed for insufficient clinical response (1.2% with varenicline vs 5.0% with placebo).

Table 7. Subject Disposition Table (Source: Study report, section 10.1, Table 9)

Number of Subjects (%)	Varenicline		Placebo	
	n	%	n	%
Screened, 1747 subjects				
All Randomized or ITT Population	760		750	
Treated	751	(98.8)	742	(98.9)
Completed treatment	540	(71.1)	492	(65.6)
Discontinued treatment	211	(27.8)	250	(33.3)
Completed study	559	(73.6)	515	(68.7)
Discontinued study	192	(25.3)	227	(30.3)
All Treated Population	751		742	
Discontinuations from study	192	(25.6)	227	(30.6)
Subject died	1	(0.1)	0	---
Relation to study drug not defined	178	(23.7)	214	(28.8)
Insufficient clinical response	6	(0.8)	28	(3.8)
Lost to follow-up	76	(10.1)	81	(10.9)
No longer willing to participate in study	54	(7.2)	59	(8.0)
Other	39	(5.2)	43	(5.8)
Protocol violation	3	(0.4)	3	(0.4)

Number of Subjects (%)	Varenicline		Placebo	
	n	%	n	%
Related to study drug	12	(1.6)	9	(1.2)
Adverse event	12	(1.6)	9	(1.2)
Not related to study drug	1	(0.1)	4	(0.5)
Adverse event	1	(0.1)	4	(0.5)
Discontinuations from treatment	211	(28.1)	250	(33.7)
Subject died	1	(0.1)	0	---
Relation to study drug not defined	146	(19.4)	198	(26.7)
Did not meet entrance criteria	1	(0.1)	0	---
Insufficient clinical response	9	(1.2)	37	(5.0)
Lost to follow-up	50	(6.7)	61	(8.2)
No longer willing to participate in study	35	(4.7)	45	(6.1)
Other	47	(6.3)	52	(7.0)
Protocol violation	4	(0.5)	3	(0.4)
Related to study drug	53	(7.1)	40	(5.4)
Adverse event	53	(7.1)	40	(5.4)
Not related to study drug	11	(1.5)	12	(1.6)
Adverse event	11	(1.5)	12	(1.6)

The Full Analysis Set was referred to as the Intent-to-Treat (ITT) population and included subjects who were randomized to study treatment. The All Treated population included all subjects who had been randomized and received at least 1 dose, including partial doses, of randomized study medication.
Abbreviations: N = number of subject in the treatment group; n = number of subjects per category.
Source: Section 14.1, Tables 14.1.1.1.1, 14.1.1.2, and 14.1.1.4.

Protocol Violations/Deviations

The table below describes the clinically significant protocol deviations by treatment arm. The most relevant types of protocol violations are those involving enrollment of patients with CO concentration < 10 ppm at baseline (indicating they were not current smokers), and those involving use of prohibited concomitant smoking cessation treatments or nicotine. Four subjects in the varenicline group and two in the placebo group had CO concentrations < 10 ppm. None of them were responders for any of the endpoints; this does not affect interpretation of the study. The use of nicotine replacement, e-cigarettes, or other prohibited smoking cessation products (including non-study varenicline) could also influence the outcome. A total of 51 subjects had violations of this nature. By comparing the timing of the protocol violation report and the responder status at the same point, the reviewer was able to confirm the applicant's coding of responder status was appropriate. Therefore, these violations have no effect on the reviewer's interpretation of the study results.

Table 8. Clinically Significant Protocol Deviations: All Randomized Subjects (Source: Module 2 Summaries, Table sC1.1 and sC1.2)

	Varenicline (760 subjects, 40 subjects with protocol deviation)		Placebo (750 subjects, 44 subjects with protocol deviation)	
Category of Deviation	Number of Deviations	Number of Unique Subjects	Number of Deviations	Number of Unique Subjects
Allergic Reaction	1	1		
CO Concentration at Screening ≤ 10 ppm	4	4	2	2
IP administration/ study treatment*	1	1	0	0
Inclusion/Exclusion criteria	1	1	0	0
Prohibited Concomitant Medications	3	2	3	3
Prohibited Medical History	11	11	8	8
Prohibited Concomitant medication: Electronic cigarette/NRT	20	20	31	31

*Varenicline subject 10281009 received the wrong bottle number, which resulted in placebo dosing for Week 1.
Abbreviations: CO = carbon monoxide; IP = investigational product; NRT = nicotine replacement therapy

Table of Demographic Characteristics

Demographic characteristics for treated subjects in the study are summarized in the table below and were well balanced between the 2 treatment groups. The majority of treated subjects in the varenicline and placebo groups were white (62.7% and 61.3%, respectively), followed by Asian ethnicity (23.3% and 23.9%, respectively). Approximately 56% of the subjects were male (56.1% and 56.7%, varenicline, and placebo groups, respectively). In the varenicline group, subjects ranged in age from 19 to 79 years with a mean BMI of 26.8 kg/m2. In the placebo group, subjects ranged in age from 18 to 78 years with a mean BMI of 27.0 kg/m2.

Table 9. Demographic Characteristics - All Treated Population (Source: Study report, section 11.2, Table 12)

	Varenicline (N = 751)		Placebo (N = 742)	
Age, n (%)	Male (N = 421)	Female (N = 330)	Male (N = 421)	Female (N = 321)
18-44 years	212 (50.4)	152 (46.1)	208 (49.4)	160 (49.8)
45-64 years	189 (44.9)	164 (49.7)	186 (44.2)	146 (45.5)
≥ 65 years	20 (4.8)	14 (4.2)	27 (6.4)	15 (4.7)
Mean (SD)	44.4(11.9)	45 (11.8)	44.7 (12.2)	44 (11.9)
Range	19-78	20-79	18-78	19-73
Race, n (%)				
White	217 (51.5)	254 (77.0)	229 (54.4)	226 (70.4)
Black	20 (4.8)	14 (4.2)	20 (4.8)	27 (8.4)
Asian	129 (30.6)	46 (13.9)	130 (30.9)	47 (14.6)
Other	55 (13.1)	16 (4.8)	42 (10.0)	21 (6.5)
Body Mass Index, kg/m[e]				
Mean (SD)	26.7 (5.0)	26.9 (6.6)	26.9 (5.3)	27.1 (6.7)
Range	17.2-56.2	16.5-64.3	15.8-52.6	16.2-61.6

[a] Subject (b) (6) was assigned to varenicline as a male but is in fact female.
The All Treated population which was the Safety Analysis Set included all subjects who had been randomized and received at least 1 dose, including partial doses of randomized medication.
Body mass index was defined as weight/(height x 0.01)^2.
Abbreviations: N = number of subjects in treatment group; n = number of subjects per category; SD = standard deviation.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Smoking history and Fagerström score for Nicotine Dependence for the All-Treated population are displayed in the table below.

Table 10. Smoking History and Fagerström Test for Nicotine Dependence – All Treated Population (Source: Study report, section 11.2.2, Table 13)

	Measure	Varenicline (N=751)	Placebo (N=742)
Age started smoking	Mean (SD)	17.3 (4.32)	17.3 (4.45)
Total years smoked	Mean (SD)	26.7 (12.25)	26.5 (12.17)
Average cigarettes per day			
since started smoking	Mean (SD)	18.6 (8.82)	19.0 (8.54)
In past year	Mean (SD)	10.7 (8.54)	20.7 (8.01)
In past month	Mean (SD)	20.6 (8.44)	20.8 (8.20)
Longest abstinence period, days			
Over lifetime	Mean (SD)	266.4 (695.43)	206.4 (635.10)
In past year	Mean (SD)	3.6 (11.50)	2.7 (9.58)
Last serious quit attempt(days ago)	Mean (SD)	469.1 (1162.97)	739.3 (1698.21)
Lifetime serious quit attempts, Any method[a]			
None	n (%)	129 (17.2)	158 (21.3)
One		189 (25.2)	186 (25.1)
Two		138 (18.4)	108 (14.6)
Three or more		295 (39.3)	290 (39.1)
Serious quit attempts in the past year, Any method			
None	n (%)	573 (76.3)	605 (81.6)
One		137 (18.2)	103 (13.9)
Two		22 (2.9)	18 (2.4)
Three or more		19 (2.5)	15 (2.0)
Nicotine Dependence: Fagerström Test	n Mean (SD) Range	750 5.5 (2.08) 0-10	741 5.6 (2.03) 0-10

The All Treated population which was the Safety Analysis Set included all subjects who had been randomized and received at least one dose, including partial doses, of randomized medication. Percentages were based on the number of subjects with non-missing responses to the given question. [a]Calculated field, which represented the number of quit attempts and/or types used. Abbreviations: N = number of subjects in treatment group; n = number of subjects with the given response; SD = standard deviation.

The mean age at which subjects started smoking was identical in the varenicline and placebo groups (17.3 years) and the mean number of years for which the subjects had smoked was similar (26.7 and 26.5 years, respectively). The mean number of cigarettes smoked per day was also similar in both treatment groups, whether this was assessed since the subject started smoking (18.6 and 19.0 per day, varenicline and placebo groups, respectively), or over the last

year (20.7 per day in both groups) or the last month (20.6 vs 20.8 per day, varenicline vs placebo groups, respectively) prior to Baseline.

In the past year, the majority of subjects in both the varenicline and placebo groups had made no attempt to quit smoking (76.3% vs 81.6%, respectively). Based on lifetime serious attempts to quit smoking, the majority of subjects in the varenicline and placebo groups had made a serious attempt to quit smoking (82.8% vs 78.7%, respectively). The most common methods used were cold turkey (51.8% vs 48.6%, respectively) and nicotine patches (26.0% vs 24.4%, respectively). The mean longest period of abstinence since the subject starting smoking was longer in the varenicline than the placebo group (266.4 vs 206.4 days, respectively). However when focusing on the last year prior to Baseline, the mean longest period of abstinence was similar in the 2 treatment groups (3.6 vs 2.7 days, respectively). The last serious attempt to quit smoking was more recent for subjects in the varenicline group than in the placebo group (mean values of 469.1 vs 739.3 days prior to Baseline, respectively).

Subjects in the varenicline and placebo groups had frequent contact with someone who smoked (76.0% and 79.8%, respectively), although less than half of subjects in each group lived with someone who smoked (41.5% and 40.3%, respectively).

The mean Fagerström total score was similar for subjects in the varenicline and placebo groups and consistent with moderate dependence (5.5 vs 5.6, where a higher score indicates greater dependence; range is 0-10).

Responses to the individual questions indicated that nicotine dependence was similar between treatment groups. Overall, approximately 37% of subjects smoked their first cigarette of the day within 5 minutes of waking, and by 30 minutes of waking, approximately 41% of subjects have had their first cigarette of the day. The majority of subjects in both groups smoked 11 to 20 cigarettes per day; most of the remaining subjects smoked 21 to 30 cigarettes per day. Overall, these indicators suggest a population of only moderate level of tobacco dependence.

Similar proportions of subjects in the varenicline and placebo groups reported ≥1 disease or syndrome that occurred prior to the study (56.6% vs 55.5%, respectively) or that was ongoing at Baseline (75.1% vs 74.4%). The most common (≥5% of subjects in either the varenicline or placebo group) diseases or syndromes ongoing at Baseline were hypertension (13.2% vs 15.4%, respectively), back pain (10.5% vs 6.7%, respectively), headache (9.5% vs 9.3%, respectively), seasonal allergy (9.3% vs 8.8%, respectively), insomnia (7.6% vs 7.4%, respectively), hypercholesterolemia (6.7% vs 5.3%, respectively), hyperlipidemia (5.7% vs 6.6%, respectively), asthma (5.3% vs 4.7%, respectively), and gastroesophageal reflux disease (3.7% vs 5.8%, respectively). See table below.

Table 11. Most Common Diseases or Syndromes at Baseline Disease in ≥ 5% of Subjects (Source: Study report, section 11.2.3)

Disease/Syndrome	Varenicline (%)	Placebo (%)
Hypertension	13.2	15.4
Back pain	10.5	6.7
Headache	9.5	9.3
Seasonal allergy	9.3	8.8
Insomnia	7.6	7.4
hypercholesterolemia	6.7	5.3
hyperlipidemia	5.7	6.6
Asthma	5.3	4.7
Gastroesophageal reflux	3.7	5.8

Subjects were excluded from the study if they had a history of a suicide attempt or any suicidal behavior in the past 2 years prior to Screening, assessed using the C-SSRS and/or the SBQ-R. Subjects were also excluded if they had suicidal ideation identified ("yes" to Questions 4 and/or 5 on the C-SSRS) by the C-SSRS at the Screening or Baseline visit.

At Screening, most subjects in the varenicline and placebo groups reported that they had never thought about (or attempted) killing themselves (86.4% vs 86.6%, respectively). When asked if they had ever told someone else that they were going to (or might) commit suicide, the majority in both groups reported that they had not (96.1% vs 97.7%); of the remaining subjects, 37 subjects (23 and 14 subjects, respectively) had responded "yes, at one time, but did not really want to die" and 2 subjects in the varenicline group responded "yes, more than once, but did not want to do it".

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Assessments of treatment compliance were performed as described in the protocol. Subjects were to return bottles at each visit and a dosing record and drug accountability form was completed. Subjects who had at least 80% treatment compliance, i.e., took 1 dose (partial or full) of study treatment for at least 80% of the nominal duration of the active treatment phase were included in the Completer population.

A greater number of subjects in the varenicline group than in the placebo group were treated for 151 days or more (538 of 751 subjects vs 488 of 742 subjects, respectively). The median duration of treatment was similar in both treatment groups (167.0 vs 166.0 days, respectively).

Concomitant drug treatments were used by 78.6% of subjects in the varenicline group and 75.2% of subjects in the placebo group. The most frequently reported concomitant treatments

were similar in the varenicline and placebo groups: ibuprofen (120 and 131 subjects, respectively), acetylsalicylic acid (55 and 49 subjects, respectively), amoxicillin (48 and 45 subjects, respectively), and paracetamol (107 and 89 subjects, respectively).

Efficacy Results – Primary Endpoint (summary from study report)

The ITT population was the primary analysis set for the efficacy analyses in this study. The primary efficacy endpoint for this study was CO-confirmed 10-week continuous abstinence for Weeks 15 through 24, inclusive. Responders for this endpoint reported no smoking and no use of any other nicotine-containing product since the last study visit/contact on the NUI and did not have expired CO >10 ppm at any time point during Weeks 15 through 24, inclusive.

The treatment-by-center interaction was investigated with the interaction tested at the 0.05 significance level for the primary and key secondary endpoints.

For the statistical analysis of the key primary endpoint, continuous abstinence rate from Weeks 15 through 24, no significant interaction between treatment and pooled center was found for ITT population. Similar results were observed in the All Treated population and Completers population. Consequently, the treatment effect can be generalized for all sites (countries).

Table 12. CO-confirmed Continuous Abstinence Rate from Weeks 15-24 (Source: Pfizer study report, Section 11.4.1,Table 15)

	Varenicline		Placebo		OR (95% CI) vs	p-value vs
Analyses Set	N	n (%)	N	n (%)	Placebo	Placebo
ITT Population	760	244 (32.1)	750	52 (6.9)	8.74 (6.09, 12.53)	<0.0001
All Treated Population	751	244 (32.5)	742	52 (7.0)	8.74 (6.09, 12.55)	<0.0001
Completer Population	564	225 (39.9)	513	45 (8.8)	9.78 (6.55, 14.60)	<0.0001

The Intent-to-Treat population included all randomized subjects. The All Treated population included all subjects who had been randomized and received at least one dose, including partial doses, of randomized study medication. The Completer population included all randomized subjects who took at least one dose (partial or full) of study treatment for at least 80% of the nominal duration of the active treatment phase of study.
The odds ratios and p-values were obtained from a logistic regression model including the main effects of treatment and pooled center.
Abbreviations: CI = confidence interval; CO = carbon monoxide; ITT = Intent-to-Treat; N = number of subjects in the analysis set; n = number of subjects who, at each visit from Week 15-24 (inclusive), reported no smoking and no use of other nicotine-containing products since the last study visit/last contact (on the Nicotine Use Inventory) and who did not have CO >10 ppm at any of these visits; OR = odds ratio; ppm = parts per million.
Source: Section 14.2, Tables 14.2.2.1.1, 14.2.2.1.2, and 14.2.2.1.3.

For the primary endpoint (ITT population, table 12 below), subjects treated with varenicline had a significantly higher continuous abstinence rate compared with placebo between Weeks 15 and 24 (32.1% vs 6.9%; OR [95% CI]: 8.7 [6.09, 12.53]; p < 0.0001]).

As sensitivity analyses to the primary endpoint (ITT population), the All Treated and Completer populations were also investigated.

For the All Treated population, subjects treated with varenicline had a significantly higher continuous abstinence rate compared with placebo between Weeks 15 and 24 (32.5% vs 7.0%; OR [95% CI]: 8.74 [6.09, 12.55]; p<0.0001).

For the Completers population (Table 15), subjects treated with varenicline had a significantly higher continuous abstinence rate compared with placebo between Weeks 15 and 24 (39.9% vs 8.8%; OR [95% CI]: 9.78 [6.55, 14.60]; p<0.0001).

Data Quality and Integrity – Reviewers' Assessment

The submission was adequately organized and did not present barriers to review.

Efficacy Results – Secondary and other relevant endpoints

The key secondary efficacy endpoints were the continuous abstinence during the last 4 weeks of treatment (from Weeks 21 through 24) and the long-term continuous abstinence (from Weeks 21 through 52), both confirmed by expired CO ≤10 ppm. Results are displayed in the table below.

Table 13. CO-confirmed Continuous Abstinence Rates from Weeks 21 through 24 and from Weeks 21 through 52 (Source: Study report, section 11.4.2, Table 16)

	Varenicline		Placebo		OR (95% CI)	p-value vs
Analyses Set	N	n (%)	N	n (%)	vs Placebo	Placebo
CAR 21-24						
ITT Population	760	287 (37.8)	750	94 (12.5)	5.66 (4.21, 7.61)	<0.0001
All Treated Population	751	287 (38.2)	742	94 (12.7)	5.67 (4.21, 7.63)	<0.0001
Completer Population	564	266 (47.2)	513	83 (16.2)	6.27 (4.50, 8.72)	<0.0001
CAR 21-52						
ITT Population	760	205 (27.0)	750	74 (9.9)	4.02 (2.94, 5.50)	<0.0001
All Treated Population	751	205 (27.3)	742	74 (10.0)	4.03 (2.95, 5.51)	<0.0001
Completer Population	564	190 (33.7)	513	67 (13.1)	4.00 (2.85, 5.62)	<0.0001

The Intent-to-Treat population included all randomized subjects. The All Treated population included all subjects who had been randomized and received at least 1 dose, including partial doses, of randomized study medication. The Completer population included all randomized subjects who took at least 1 dose (partial or full) of study treatment for at least 80% of the nominal duration of the active treatment phase of study.
The odds ratios and p-values were obtained from a logistic regression model including the main effects of treatment and pooled center.
Abbreviations: CAR = continuous abstinence rate; CI = confidence interval; CO = carbon monoxide; ITT = Intent-to-Treat; N = number of subjects in the analysis set; n = number of subjects who, at each visit from Weeks 21 through 24 (inclusive) or Weeks 21 through 52 (inclusive), respectively, reported no smoking and no use of other nicotine-containing products since the last study visit/last contact (on the Nicotine Use Inventory) and who did not have CO >10 ppm at any of these visits; OR = odds ratio; ppm = parts per million.

Since the test for the treatment-by-center interaction was not significant for the primary endpoint, the test of the interaction term for the key secondary endpoints was not required as per the fixed-sequence procedure.

For the key secondary endpoints (ITT population), subjects treated with varenicline had a significantly higher continuous abstinence rate compared with placebo between Weeks 21 and 24 (37.8% vs 12.5%; OR [95% CI]: 5.66 [4.21, 7.61]; p<0.0001) and between Weeks 21 and 52 (27.0% vs 9.9%; OR [95% CI]: 4.02 [2.94, 5.50]; p<0.0001).

Dose/Dose Response

Only the approved dose was explored. Therefore, no additional dose response analyses were conducted.

Efficacy Summary

The results of this study demonstrate that Chantix is effective as an aid to smoking cessation in smokers who are not willing or able to make an abrupt quit attempt, but who were willing to follow a reduce-to-quit schedule with the goal of abstinence by Week 12. Additional analyses were conducted by Ms. Kate Meaker, M.S., Division of Biometrics II. The findings below are excerpted from Ms. Meaker's review.

The efficacy endpoints were tested using a logistic regression model with terms for treatment group and center. In order to preserve the Type I family-wise error rate of 0.05, a step-down procedure was used for the analysis of the primary and secondary endpoints. The order of testing was 1) the CAR for weeks 15-24; 2) CAR for weeks 21-24; and 2) CAR for weeks 21-52. Each comparison was tested at α=0.05.

On both the primary and secondary efficacy endpoints, the varenicline treatment group was statistically significantly better than the placebo treatment group (p<0.001). Table 15 presents the applicant's results. The applicant's analyses were conducted as planned in the protocol. The statistics reviewer was able to replicate the applicant's efficacy analysis results.

Table 14. Efficacy Analysis Results (Statistics Review, Table 3)

All Subjects	Varenicline	Placebo	Odds Ratio (95% CI)	p-value
Primary: Continuous Abstinence Rate Weeks 15-24	244/760 32%	52/750 7%	8.7 (6.1, 12.5)	p<0.001 [a]
Continuous Abstinence Rate Weeks 15-52	182/760 24%	45/750 6%	6.0 (4.2, 8.7)	p<0.001 [a]
Secondary: Continuous Abstinence Rate Weeks 21-24	287/760 38%	94/750 13%	5.7 (4.2, 7.6)	p<0.001 [a]
Secondary: Continuous Abstinence Rate Weeks 21-52	205/760 27%	74/750 10%	4.0 (2.9, 5.5)	p<0.001 [a]

Source: Statistics Review Table 3, Clinical Study Report Table 15, and SAS datasets
[a] The odds ratios and p-values were obtained from a logistic regression model including the main effects of treatment and pooled center.

As noted in a previous section on financial disclosures, 5 of the 215 clinical investigators (sites listed in the study report had financial information to disclose, receiving payments exceeding

the threshold amount of $24,999.00, which represents 2.33% of the total number of all clinical investigators who participated in the study. These include: [redacted], site [redacted]) $180,000, [redacted], site [redacted]- $109,256.69, [redacted] site [redacted] - $102,000, [redacted], site [redacted])- $28,391, and [redacted], site [redacted]), $33,628.50.

Each site enrolled 16-34 subjects for a total of 125 subjects (62 varenicline and 63 placebo), the efficacy results did not differ notably from the findings at other sites (Table 7). The Sponsor noted that all Investigator Initiated Research Grants associated with clinical investigators are paid directly to the Institution rather than to the individual clinical investigator.

Table 15. Efficacy Analysis Excluding Sites [redacted] (Statistics Review Table 4)

	Varenicline	Placebo	Odds Ratio (95% CI)	p-value
Continuous Abstinence Rate Weeks 15-24	222/698 32%	51/687 7%	8.0 (5.5, 11.6)	p<0.001 [a]
Continuous Abstinence Rate Weeks 15-52	163/698 23%	45/687 7%	5.3 (3.6, 7.7)	p<0.001 [a]
Continuous Abstinence Rate Weeks 21-24	262/698 38%	92/687 13%	5.2 (3.8, 7.0)	p<0.001 [a]
Continuous Abstinence Rate Weeks 21-52	185/698 27%	74/687 11%	3.5 (2.6, 4.8)	p<0.001 [a]

Source: Statistics Review Table 4, and SAS datasets
[a] The odds ratios and p-values were obtained from a logistic regression model including the main effects of treatment and pooled center.

Ms. Meaker reviewed exploratory analyses for the primary endpoint by age groups, gender, race, and region. The only notable difference in the subgroup tables is that both treatment arms had lower responder rates in North America than in Europe or the Asia/Pacific region. In each region, the varenicline group had a higher rate of success than the placebo group. Table 16 below, from Ms. Meaker's review, show the results of these analyses.

These are descriptive analyses only and are not intended for inferential purposes. The varenicline treatment group consistently showed a higher continuous abstinence rate than the placebo group.

Table 16. Subgroup Analyses: Age, Gender, Race and Region (Statistics Review, Table 5)

Primary Endpoint: Continuous Abstinence Rate Weeks 15-24		
	Varenicline N=760	**Placebo N=750**
Age group		
≤ 65 years	232/725 (32%)	48/708 (7%)
> 65 years	12/35 (34%)	4/42 (10%)
Gender		
Female	109/335 (33%)	18/324 (6%)
Male	135/425 (32%)	34/426 (8%)
Race		
Caucasian	152/476 (32%)	23/463 (5%)
Non-Caucasian	92/284 (32%)	29/287 (10%)
Region		
Asia / Pacific Islands	90/216 (42%)	26/211 (12%)
Europe	75/203 (37%)	12/203 (6%)
North America	79/341 (23%)	14/336 (4%)
Total	244/760 32%	52/750 7%

Discussion and Recommendations

There are many possible "windows" for calculating and reporting quit rates. Currently, CDER's advice is that the study should show that more smokers achieve abstinence within a pharmacologically-justified grace period, and maintain it through the period of treatment, when treated with active drug than when treated with placebo. If the effect of the treatment is not expected immediately due to mechanism of action, pharmacokinetics, or other factors, then efficacy ascertainment may take place over a period following a "grace period." In a reduce-to-quit study, the entire reduction process is part of the "grace period."

Clinical Review
Sarah Arnold, M.D., M.P.H.
NDA Supplement 039
Chantix (varenicline)

Historically, for smoking cessation, six-week trials were considered conventional, and the ascertainment window was set at weeks 2-6, somewhat arbitrarily. However, this trial duration was appropriate for nicotine replacement products, which were assumed to treat a self-limiting condition (acute nicotine withdrawal), and more recently, the clinical approach to smoking cessation treatment has been moving toward viewing the disorder of tobacco dependence as a chronic, relapsing condition, and a longer-term approach to treatment has been more common. Initially, some trials were proposed that employed an efficacy ascertainment window of weeks 2-6 in the midst of a longer period of treatment, in an effort to meet the "agency standard." The Agency articulated the view that relapse during ongoing treatment would not be regarded as treatment success, and advised that a "last four weeks of treatment" window would be more suitable. This was the analytic approach specified in the protocols for the initial varenicline studies.

However, the Division's thinking has evolved as longer and longer treatment durations have been proposed, sometimes resulting in a grace period of many months and an efficacy ascertainment period of four weeks. Ultimately, the concept of "abstinence throughout treatment following a pharmacologically-justified grace period" was articulated in a White Paper and has been communicated to sponsors of ongoing development programs.

The original varenicline trials were 12 weeks in duration and the efficacy ascertainment period was set at the last four weeks, specifically Weeks 9-12. This is the quit rate included in labeling. It can be argued that the partial agonist properties of varenicline might result in blockade of exogenous nicotine, allowing for an extinction approach to behavior change; nevertheless the efficacy of varenicline is apparent even without the prolonged grace period applied. On the other hand, there are often subjects who require several weeks to initiate abstinence; thus, the antagonist properties of the drug and an extinction mechanism of action may play and important role in varenicline's efficacy.

However, in the case of the reduce-to-quit study, there does not seem to be a strong argument for applying an additional prolonged grace period after the protocol-specified quit date. The protocol-specified primary analysis, is, appropriately, the window of Week 15 (allowing a brief 2 weeks of grace beyond the quit date) through the end of treatment (Week 24). A secondary window of "last four weeks of treatment" (Weeks 21-24) was included in the protocol but on further consideration it does not seem justified. Pfizer has proposed inclusion of this rate in the label but it does not add additional information and should not be included. Instead, the Weeks 15-24 (2 weeks' grace through end-of-treatment) and Weeks 15-52 (2 weeks' grace through end-of-observation) are the more informative rates and should be included. Varenicline was significantly superior to placebo on both of these measures.

Given the longstanding question of whether quitting by gradual reduction is or is not a suitable and effective method of quitting smoking, we considered it important to determine whether

the patients who quit smoking in this trial actually did so gradually. The primary outcome can be seen as a composite of successful abrupt quitters and gradual quitters. As with other composite endpoints, it is necessary to explore the effect of the drug on components of the composite before allowing a new claim. Additional explorations by Ms. Meaker revealed that approximately 8% of the Chantix-treated subjects vs. approximately 0.5% (four individuals) of the placebo-treated subjects quit abruptly and met criteria for quit by Week 4. Of these, 66% of the Chantix-treated and half of the placebo-treated subjects ultimately sustained abstinence through the end of the observation period. These represent a small subset of the total successful quitters, suggesting that it is appropriate to conclude that the subjects in this trial who quit smoking mainly did so by gradual reduction and not abruptly, although few appeared to take the entire recommended period to do so.

The findings in the placebo group may be interpreted as confirmation that the RTQ method is not a very good method by itself. Although the population was selected on the basis of being "unwilling or unable" to quit abruptly, it is not clear why the participants felt unwilling or unable to quit; they were, overall a low-dependency group with few, sometimes no, previous quit attempts. Nonetheless, the overall four-week quit rate was extremely low in the placebo group—less than half the historical placebo rate for other Chantix studies. It is difficult to know whether this represents the reluctance or recalcitrance of the population, or the lack of effectiveness of the method. However, because RTQ is typically recommended only to those who self-identify as unwilling to attempt abrupt cessation, the findings are relevant in either case. Notably, the Chantix-attributable rate of four-week quitting success is about the same in this study as in previous studies in more quit-ready smokers. The gradual reduction method should probably not be recommended to smokers who feel they are ready or able to quit abruptly, whether with or without pharmacologic support; however, for those who are willing to attempt cessation only on a gradual basis, the method works much better with Chantix than without it.

7 Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

There is only one trial relevant to this treatment paradigm, so no integrated review of effectiveness was performed

8 Review of Safety

Deleted Sections

- No data was submitted to inform a discussion of Sub-sections 8.7 Additional Safety Explorations, 8.7.1 Human Carcinogenicity or Tumor Development, 8.7.2 Human Reproduction and Pregnancy, 8.7.3 Pediatrics and Assessment of Effects on Growth, and 8.7.4 Overdose, Drug Abuse Potential, Withdrawal, and Rebound and these sections were deleted.
- Sub-section 8.4.10 was deleted because there are no immunogenicity concerns to discuss.
- Section 8.10 was deleted because this is a review of a single efficacy study.

8.1. Safety Review Approach

This supplemental application includes the results of one study in a population of patients who were not willing or able to quit smoking within the next month but were willing to attempt to reduce their smoking to work toward a quit attempt within the next 3 months, and an updated integrated summary of safety providing pooled analyses of all completed controlled trials.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

All patients were assigned to the same dose regimen, but compliance was variable among participants. The duration of exposure to study drug is summarized in Pfizer's Table 14.4.1, reproduced below:

Table 17. Duration of Treatment - All Treated Population

Number of Subjects	Varenicline (N=751)	Placebo (N=742)
Duration Category (Days)		
≤1	2	1
2-7	6	7
8-14	22	21
15-28	26	15
29-60	55	80
61-90	24	48
91-120	31	37
121-150	47	45
≥151	538	488
Median Duration	167.0	166.0
Range	1-204	1-189

All Treated Population (N) included all subjects who have been randomized and received at least 1 dose, including partial doses, of randomized study medication.
NOTE: The duration was defined as the total number of dosing days from the first to and including the last day of each treatment.

The median duration of varenicline treatment was 167 days compared with 166 days for placebo treatment. The duration of treatment ranged from 1 to 204 days for varenicline compared with 189 days for placebo.

8.2.2. Relevant characteristics of the safety population:

See section 6, tables 9, 10, and 11.

8.2.3. Adequacy of the safety database:

Demographics and baseline characteristics were presented in section 6. The safety population is an adequate representation of the target treatment population of smokers who are unwilling or unable to make an abrupt quit attempt.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

Data integrity and submission quality were adequate for this review.

8.3.2. Categorization of Adverse Events

All adverse events reported through Week 52 were coded using MedDRA v16.1. Events were recorded using only an "investigator verbatim" term, with no further detail on the case report form, unless further details were provided by Pfizer at Division request.

8.3.3. Routine Clinical Tests

Scheduled central laboratory tests were not performed after screening. See section 8.4.

8.4. Safety Results

8.4.1. **Deaths**One death was reported in this study. A 72- year-old male subject who was smoking 40 cigarettes per day at the baseline visit ([redacted] 2012) was found dead of unknown causes. The Sponsor coded this to the term "fatal event" and assigned the event to Day 8 (imputed from incomplete dates and times). There was no documented relevant past psychiatric history, and he was using no other nicotine products. The CSSRS recorded no previous lifetime suicidal ideation or behavior and no suicidal ideation or behavior during his limited participation in the study. The subject was randomized to varenicline and received the first dose at his baseline visit on [redacted] 2012. The subject's last clinic visit was on [redacted] 2012. The subject missed his week 2 study visit on [redacted] 2012. Several unsuccessful attempts were made to contact him, his neighbors reported him missing for a number of days. The police found him dead in his kitchen. No autopsy was done to confirm the date of death or its causes. No toxicology reports or laboratory reports were provided. The subject's baseline labs on 9 February 2012 were unremarkable. Although the investigator reported the event was unrelated to varenicline treatment, the review division determined the relationship of this death to the study drug could not be ruled out.

According to the integrated summary of safety, across all 19 placebo-controlled studies completed as of 31 December 2014, there were 17 deaths (10 varenicline, 7 placebo). Except for the death in this current study (Reduce-to-Quit, RTQ), all deaths occurred after the subjects had stopped treatment and for the majority of subjects, the onset of the event(s) with a fatal outcome was more than 30 days post therapy.

8.4.2. Serious Adverse Events

Across the entire 52-week study, according to Pfizer, the percentage of subjects with solicited and volunteered all-causality SAEs was higher with varenicline treatment than with placebo treatment (34 [4.5%] vs 23 [3.1%], respectively). The percentage of subjects with treatment-emergent solicited and volunteered all-causality SAEs was higher with varenicline treatment than with placebo treatment (28 [3.7%] vs 16 [2.2%], respectively).

Most of the AEs that meet the criteria of serious in the safety database occurred post-therapy or did not require a change in dose, and with the exception of 2 events, most events were considered by the sponsor to be unrelated to the study drug: treatment-related SAEs of presyncope and gastritis were reported for 1 subject each in the varenicline group; the sponsor reports no treatment-related SAEs in the placebo group.

Table 18 is comprised only of reported SAEs in which relationship to study drug could not be ruled out by the reviewer. Events that had other clear causes, or occurred after week 26 (day 172, two weeks after last day of medication) were removed, as these were not considered to be treatment-emergent. These SAEs are consistent with those previously reported in prior studies.

Table 18. Serious Adverse Events-All Treated Population (review of Pfizer's Table 14.3.2.2)

Varenicline				Placebo			
Subject	Adverse Event	Brief Description	Onset (Trial Day)	Subject	Adverse Event	Brief Description	Onset (Trial Day)
36 yo M (b) (6)	Depression Suicidal ideation	10 days after start of study drug, subject reported sxs of depression, 10 days later, depression worsened to Suicidal ideation and subject was hospitalized for 10 days. Study drug was continued (106 days treatment)until subject withdrew from study, was "unwilling to participate"	21	50 yo F (b) (6)	Depression, hallucinations, Subarachnoid Hemorrhage	Subject experienced depression one month after study drug started, study drug continued, 2 months into study, subjected experienced hallucination, resolved one day later, continued study drug, several weeks later, subject had ruptured cerebral aneurysm, study drug was withdrawn after 123 days of treatment.	110
40 yo F (b) (6)	Suicide attempt	Subject had h/o depression on escitalopram, while on study drug for 35 days, she had migraine, treated as outpatient, study drug continued. Subject's depression worsened 3 months later, and evolved into suicidal ideation and intentional self-injury, suicide attempt, taking extra alprazolam (had from prior treatment). Study drug was withdrawn after 145 days of treatment.	35	45 yo F (b) (6)	Depression, suicidal ideation, Alcoholism	Subject had moderate depression one month into the study, drug was continued. At week 8, subject expressed non-specific active suicidal thoughts without plan, which persisted through week 12, when subject was hospitalized for alcoholism, study drug was discontinued at the time of hospitalization.	79
30 yo M (b) (6)	Seizure	h/o insomnia, being treated with brotizolam and flunitrazepam, amobarbital, and perphenazine. Subj had seizure, had evaluation at hospital, was treated for seizure, study drug continued for 166 days.	132	33 yo F (b) (6)	Vertigo and Vomiting	Subject experienced severe vertigo and vomiting, was hospitalized for 4 days, receiving IV fluids. Study drug withdrawn, subject withdrawn from study	85
51 y/o M (b) (6)	Hypertensive crisis	Subject was hospitalized for hypertensive crisis for 6 days, study drug continued. Subject was also treated for alcohol abuse with potassium, thiamine and carbamazepine, and psychotherapy, study drug was continued.	119 81	47 yo M (b) (6)	Myocardial Infarction	Subject sustained MI, was hospitalized for angioplasty, stent placement, subject permanently discontinued study	35

51 yo M (b) (6)	Aortic aneurysm	10 days into study, pt had presyncopal event requiring evaluation, no change in drug dose. Drug discontinued day 157 due to aortic aneurysm rupture.	10	53 yo F (b) (6)	Myocardial Infarction	Subject experienced myocardial infarction , was hospitalized for treatment, drug was permanently discontinued after 99 days of treatment.	99
45 yo M (b) (6)	Supraventricular tachycardia	Supraventricular tachycardia requiring adenosine, no change in drug dose.	53	32 yo F (b) (6)	Diabetes	Subject had hypertension, inadequate control of diabetes, and a diabetic foot ulcer, study drug temporarily stopped, events resolved and study drug was re-started for total treatment of 141 days.	33
57 yo M (b) (6)	Hypertensive crisis	Subject had chronic HTN controlled on metoprolol, 2 episodes of hypertensive crisis, had to add 2 more medications, study drug not withdrawn, was taken for 151 days. Pt withdrew from study during follow-up phase, "no longer willing to participate"	155	67 yo F (b) (6)	Peripheral artery disease	Subject was hospitalized for peripheral arterial disease, had angioplasty, subject permanently discontinued study after 84 days of treatment.	85
66 yo M (b) (6)	Angina pectoris	Subject had episode of angina, treated with NTG, and coronary artery stent. Study drug withdrawn at day 144.	133	42 yo F (b) (6)	Ileus	Subject with h/o GERD, esophageal neoplasm, had ileus, which was treated and condition resolved 6 days later, no action taken with study drug.	112
58 yo M (b) (6)	Pancreatic cyst	pancreatic cyst, MRI confirmed benign pancreatic neoplasm, requires pancreatin for pancreatic insufficiency, also had panic attack, study drug withdrawn	95	34 yo M (b) (6)	Chest pain	Chest pain due to lower respiratory tract infection, was hospitalized and treated. Drug was not withdrawn.	150
47 yo M (b) (6)	Gastritis	Subject with h/o GERD, on omeprazole. After 20 days on study drug, pt had gastritis, study drug dose was decreased. Pt had second episode of gastritis, study drug was discontinued after 135 days of treatment.	139	42 yo M (b) (6)	Costochondritis	2 months into the study, subject experienced chest wall pain and mild bronchitis, which resolved with antibiotics. No action taken with drug. Treated for 172 days.	146
57 yo F (b) (6)	Unstable angina, Chest pain, musculoskeletal	musculoskeletal chest pain and unstable angina with anxiety, hospitalized for work-up, study drug discontinued	120	44 yo M (b) (6)	Traumatic injuries (MVA)	Subject sustained pneumothorax, chest contusion and rib fracture in traffic accident, for which he was hospitalized. Subject's daughter died during the study, and he discontinued the study for reasons of bereavement after 100 days of treatment.	64

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

The table below shows reasons for discontinuation. Similar terms (depression/depressed mood) were combined. Depression was the reason for discontinuation in 15 (2.0) of varenicline-treated subjects and 9 (1.2) of placebo-treated subjects. Suicidal ideation was the reason for discontinuation in 2 (0.3) in both groups. According to the integrated safety summary, a higher proportion of both varenicline and placebo subjects in this study (Reduce-to-Quit) had AEs leading to dose reduction or temporary discontinuations compared to the 2 pooled cohorts (all-causality AEs: varenicline: 19.2% RTQ Study vs 8.2% 18-Study cohort and 9.6% 19-Study cohort; placebo: 9.7% vs 4.7% and 5.6%, respectively). According to Pfizer, a possible explanation for this higher proportion of AEs leading to dose reduction or temporary discontinuation in this study (Reduce-to-Quit), is the doubling of the treatment duration and consequently, of the observation period, to 24 weeks in this study versus 12 weeks or less in 17 of the 18 studies included in the 18-study cohort. This is supported by the fact that the rate of dose reduction or temporary discontinuation for this study was approximately double in the placebo group, as well as the varenicline group.

Table 19. Discontinuations due to Adverse Events (Prepared by Reviewer AE datasets)

	Varenicline (%)	**Placebo** (%)
	N = 751	N = 742
PSYCHIATRIC DISORDERS		
Suicidal ideation	2 (0.3)	2 (0.3)
Intentional self-injury	1 (0.1)	0 (0)
Insomnia/sleep disorder	2 (0.2)	5 (0.7)
Abnormal dreams/nightmares	1(0.1)	3 (0.4)
Libido decreased	0 (0)	1 (0.1)
Alcoholism	0 (0)	1 (0.1)
Tobacco abuse	0 (0)	1 (0.1)
Paranoia	1 (0.1)	0 (0)
Hostility	1 (0.1)	0 (0)
Mood altered/mood swings	3 (0.4)	0 (0)
Depression/depressed mood	15 (2.0)	9 (1.2)
Tearfulness	2 (0.3)	0 (0)
Restlessness	0 (0)	1 (0.1)
Stress	1 (0.1)	0 (0)
Panic attack/panic reaction	2 (0.3)	2 (0.3)
Anxiety	4 (0.5)	1 (0.1
Nervousness	1 (0.1)	0 (0)
NERVOUS SYSTEM DISORDERS		

Dizziness	4 (0.4)	1 (0.1)
Dysarthria	1 (0.1)	0 (0)
Syncope	0 (0)	1 (0.1)
Tremor	1 (0.1)	1 (0.1)
Headache/cluster headache	6 (0.8)	2 (0.3)
Ruptured cerebral aneurysm	0 (0)	1 (0.1)
MUSCULOSKELETAL DISORDERS		
Musculoskeletal chest pain	1 (0.1)	0 (0)
Intervertebral disc protrusion	0 (0)	1 (0.1)
METABOLISM/NUTRITION DISORDERS		
Decreased appetite	0 (0)	2 (0.3)
INVESTIGATIONS (Liver Function abnl)	2 (0.3)	0 (0)
INFECTIONS/INFESTATIONS		
HIV infection	0 (0)	2 (0.3)
Nasopharyngitis	1 (0.1)	0 (0)
Peritonitis	0 (0)	1 (0.1)
GENERAL DISORDERS		
Asthenia	1 (0.1)	0 (0)
Fatigue	0 (0)	1 (0.1)
Chest pain	0 (0)	1 (0.1)
Irritability	5 (0.5)	3 (0.4)
GASTROINTESTINAL DISORDERS		
Dry mouth	1 (0.1)	0 (0)
Nausea	12 (1.4)	1 (0.1)
Breath odor	1 (0.1)	0 (0)
Vomiting	2 (0.2)	1 (0.1)
Flatulence	1 (0.1)	0 (0)
Abdominal pain upper	1 (0.1)	0 (0)
Dyspepsia	1 (0.1)	0 (0)
Abdominal distention	1 (0.1)	0 (0)
Diarrhoea	1 (0.1)	1 (0.1)
Gastritis	2 (0.3)	1 (0.1)
Pancreatic cyst	2 (0.3)	0 (0)
EAR AND LABYRINTH DISORDERS		
Vertigo	0 (0)	2 (0.2)
Tinnitus	0 (0)	2 (0.3)
CARDIAC DISORDERS		
Myocardial infarction	0 (0)	2 (0.2)
Angina pectoris	1 (0.1)	0 (0)
Palpitations	0 (0)	1 (0.1)

8.4.4. Significant Adverse Events

Standardized MedDRA Queries (SMQ) on 2 topics were undertaken by Pfizer, and 1 SOC was analyzed, and the results are shown below [from the Integrated Summary of Safety (ISS)]. The two SMQ topics, severe cutaneous adverse reactions (SCAR) and drug-related hepatic injury, are of common interest in pharmaceutical products, and the SOC, Psychiatric disorders, is of specific interest for varenicline. The tables show the number and percent of subjects reported events included in each of the SMQs and Psychiatric disorders SOC. The 18-study cohort refers to completed double-blind, placebo-controlled studies completed as of December 2014 excluding the current study (Protocol 3051075, Reduce-to-Quit, RTQ study). The 19-study cohort refers to all studies in the 18-study cohort plus the RTQ study.

Table 20. Severe Cutaneous Adverse Reaction SMQ (broad)

	Reduce-to-Quit Study		18-Study Cohort		19-Study Cohort	
	Var N=751	Pbo N=742	Var N=5,072	Pbo N=3,449	Var N=5,823	Pbo N=4,191
System Organ Class						
Preferred Term	number (%) of subjects					
Gastrointestinal disorders						
Mouth ulceration	2 (0.3)	0	7 (0.1)	4 (0.1)	9 (0.2)	4 (0.1)
Stomatitis	1 (0.1)	0	15 (0.3)	3 (0.1)	16 (0.3)	3 (0.1)
Infections and infestations						
Conjunctivitis	4 (0.5)	5 (0.7)	24 (0.5)	7 (0.2)	28 (0.5)	12 (0.3)
Skin and subcutaneous tissue disorders						
Blister	2 (0.3)	0	2 (<0.1)	1 (<0.1)	4 (0.1)	1 (<0.1)
Skin exfoliation	0	0	1 (<0.1)	0	1 (<0.1)	0

Source: Pfizer's ISS Table 21

The events included in the above analysis Standard MedDRA Query for Severe Cutaneous Adverse Reactions (broad) were infrequently reported in both treatment groups in the RTQ study (1.1% varenicline vs 0.8% placebo), and the pooled cohorts (18-Study cohort: 1.0% vs 0.4% and 19-Study cohort: 1.0% vs 0.5%).Few subjects discontinued treatment due to these AEs; none in the RTQ Study and less than 0.1% in both cohorts. None of these events were considered SAEs. The table above shows SCAR events reported by at least 1 varenicline subject by SOC and PT for each cohort. The most frequent SCAR PT in the RTQ study as well as both cohorts was Conjunctivitis. Most SCAR events were reported in a higher percentage of varenicline than placebo subjects; however, the overall number of subjects with events was low. There were no cases of Stevens-Johnson syndrome, erythema multiforme and toxic epidermal necrolysis. In the 18-Study cohort, 1 case of Stomatitis in a placebo subject and 2 cases of Conjunctivitis in varenicline subjects resulted in permanent treatment discontinuation.

Events coded to terms in the Drug Related Hepatic Disorders SMQ (broad) were reported in higher percentages of varenicline than placebo subjects, in the RTQ Study (0.9% varenicline vs 0.5% placebo), and in pooled cohorts (18-Study cohort: 1.7% vs 1.4% and 19-Study cohort: 1.6% vs 1.2%). Individual terms in the SMQ are shown below.

Table 21. Drug-Related Hepatic Injury SMQ (broad)

	Reduce-to-Quit Study		18-Study Cohort		19-Study Cohort	
	Var N=751	Pbo N=742	Var N=5,072	Pbo N=3,449	Var N=5,823	Pbo N=4,191
System Organ Class Preferred Term	number (%) of subjects					
Hepatobiliary disorders						
Autoimmune hepatitis	0	0	1 (<0.1)	0	1 (<0.1)	0
Chronic hepatitis	0	0	1 (<0.1)	0	1 (<0.1)	0
Drug-induced liver injury	1 (0.1)	0	1 (<0.1)	0	2 (<0.1)	0
Hepatic function abnormal	1 (0.1)	0	1 (<0.1)	2 (0.1)	2 (<0.1)	2 (<0.1)
Hepatic pain	0	0	2 (<0.1)	0	2 (<0.1)	0
Hepatic steatosis	4 (0.5)	1 (0.1)	0	0	4 (0.1)	1 (<0.1)
Hepatitis	0	0	1 (<0.1)	0	1 (<0.1)	0
Hyperbilirubinaemia	0	0	1 (<0.1)	1 (<0.1)	1 (<0.1)	1 (<0.1)
Investigations						
Blood alkaline phosphatase increased	0	0	4 (0.1)	1 (<0.1)	4 (0.1)	1 (<0.1)
Alanine aminotransferase increased	0	0	54 (1.1)	28 (0.8)	54 (0.9)	28 (0.7)
Aspartate aminotransferase increased	0	0	19 (0.4)	13 (0.4)	19 (0.3)	13 (0.3)
Blood bilirubin increased	0	0	5 (0.1)	3 (0.1)	5 (0.1)	3 (0.1)
Gamma-glutamyltransferase increased	0	0	1 (<0.1)	0	1 (<0.1)	0
Hepatic enzyme increased	0	0	8 (0.2)	3 (0.1)	8 (0.1)	3 (0.1)
Liver function test abnormal	1 (0.1)	0	7 (0.1)	4 (0.1)	8 (0.1)	4 (0.1)
Transaminases increased	0	0	2 (<0.1)	1 (<0.1)	2 (<0.1)	1 (<0.1)

Source: Pfizer's ISS Table 22

Few subjects discontinued treatment due to these AEs: 0.1% (1 varenicline subjects) in the RTQ Study, 0.4% varenicline and 0.2% placebo in the 18-Study cohort and 0.4% and 0.1% respectively, in the 19-Study cohort. In the RTQ Study, the event abnormal Liver function test (1 varenicline subject) resulted in permanent discontinuation of study treatment while in the 18-Study cohort, the events Autoimmune hepatitis (1 varenicline subject), Drug induced liver

damage (1 varenicline subject), Alanine aminotransferase increased (10 varenicline, 3 placebo subjects), Aspartate aminotransferase increased (4 varenicline, 4 placebo subjects), Blood bilirubin increased (1 varenicline subject) Hepatic enzyme increased (1 varenicline subject), and Liver function test abnormal (5 varenicline, 1 placebo subject) resulted in permanent treatment discontinuation. The Autoimmune hepatitis event was considered an SAE. A drug-related hepatic disorder event reported in more than 1 subject in the RTQ Study was Hepatic steatosis, reported in 4 (0.5%) varenicline and 1 (0.1%) placebo subjects. The most frequently reported drug-related hepatic disorder events in the 18-Study cohort were Alanine aminotransferase increased (0.4% varenicline vs 0.4% placebo). These 2 events were also most frequent in the 19-Study cohort. This is not currently described in labeling. Division of Pharmacovigilance (DPV) will be consulted to evaluate the occurrence of drug-induced liver injury (DILI) in FDA's Adverse Event Reporting System (FAERS).

Upon request from the Division, Pfizer provided revised narratives for the subject (b) (6)) in the varenicline arm of the RTQ study with abnormal liver function test that led to discontinuation from the study, and the subject (b) (6) in the same treatment arm, RTQ study with DILI. Subject (b) (6) had the abnormal liver function test that led to discontinuation from the study. At screening, the subject had normal LFTs. Apparently, the subject's general practitioner ordered another set of liver function tests (results not available), and determined that the results were elevated 2x above the upper normal limit. The subject was concerned that the study drug caused the LFT elevation, and the general practitioner recommended the subject withdraw from the study. Subject (b) (6) had the "non-serious" adverse event of drug-induced liver injury. At screening, the patient's LFTs were in normal range, except the AST/ALT, which were 41 IU/L (nl < 31 IU/L) and 95 IU/L (nl < 33 IU/L). While these levels were elevated, they were not 3 x ULN, therefore, the subject was included in the study, randomized to varenicline. No information is provided as to how DILI was diagnosed, because no further diagnostic studies or symptoms were provided. The investigator considered the event non-serious, moderate in severity. No action was taken with the study drug, and the cause of DILI was recorded as "concomitant treatment—atorvastatin." The duration of this AE was 4 days, and it apparently resolved, yet no data is provided regarding symptoms or diagnostic tests showing resolution of DILI.

Pfizer analyzed psychiatric events by reviewing events coding to the Psychiatric Disorders SOC. Table 19 below shows the psychiatric AEs at the HLGT level and individual PTs that were reported in ≥ 1% of subjects in either treatment group in any cohort. PT values in gray text did not meet the ≥ 1% criterion but are shown for comparison.

Table 22. Psychiatric SOC by HLGT with PTs reported by ≥1% in either treatment group in any cohort.

	Reduce-to-Quit Study		18-Study Cohort		19-Study Cohort	
	Var N=751	Pbo N=742	Var N=5,072	Pbo N=3,449	Var N=5,823	Pbo N=4,191
	number (%) of subjects					
Psychiatric SOC	**293 (39.0)**	**215 (29.0)**	**1,615 (31.8)**	**808 (23.4)**	**1,908 (32.8)**	**1,023 (24.4)**
High Level Group Term						
Preferred Term						
Adjustment disorders (including subtypes)	**0**	**4 (0.5)**	**1 (<0.1)**	**2 (0.1)**	**1 (<0.1)**	**6 (0.1)**
Anxiety disorders and symptoms	**79 (10.5)**	**85 (11.5)**	**253 (5.0)**	**206 (6.0)**	**332 (5.7)**	**291 (6.9)**
Agitation	20 (2.7)	14 (1.9)	52 (1.0)	32 (0.9)	72 (1.2)	46 (1.1)
Anxiety	52 (6.9)	65 (8.8)	150 (3.0)	141 (4.1)	202 (3.5)	206 (4.9)
Nervousness	10 (1.3)	9 (1.2)	29 (0.6)	24 (0.7)	39 (0.7)	33 (0.8)
Changes in physical activity	**6 (0.8)**	**12 (1.6)**	**46 (0.9)**	**31 (0.9)**	**52 (0.9)**	**43 (1.0)**
Restlessness	6 (0.8)	11 (1.5)	43 (0.8)	31 (0.9)	49 (0.8)	42 (1.0)
Cognitive and attention disorders and disturbances	**0**	**0**	**2 (<0.1)**	**3 (0.1)**	**2 (<0.1)**	**3 (0.1)**
Communication disorders and disturbances	**0**	**0**	**1 (<0.1)**	**1 (<0.1)**	**1 (<0.1)**	**1 (<0.1)**
Deliria (including confusion)	**2 (0.3)**	**1 (0.1)**	**4 (0.1)**	**2 (0.1)**	**6 (0.1)**	**3 (0.1)**
Depressed mood disorders and disturbances	**58 (7.7)**	**61 (8.2)**	**179 (3.5)**	**108 (3.1)**	**237 (4.1)**	**169 (4.0)**
Depressed mood	26 (3.5)	27 (3.6)	67 (1.3)	37 (1.1)	93 (1.6)	64 (1.5)
Depression	25 (3.3)	35 (4.7)	98 (1.9)	61 (1.8)	123 (2.1)	96 (2.3)
Dissociative disorders	**1 (0.1)**	**1 (0.1)**	**8 (0.2)**	**5 (0.1)**	**9 (0.2)**	**6 (0.1)**
Disturbances in thinking and perception	**1 (0.1)**	**2 (0.3)**	**21 (0.4)**	**10 (0.3)**	**22 (0.4)**	**12 (0.3)**
Eating disorders and disturbances	**1 (0.1)**	**0**	**1 (<0.1)**	**0**	**2 (<0.1)**	**0**
Manic and bipolar mood disorders and disturbances	**0**	**0**	**4 (0.1)**	**1 (<0.1)**	**4 (0.1)**	**1 (<0.1)**
Mood disorders and disturbances NEC	**52 (6.9)**	**40 (5.4)**	**347 (6.8)**	**206 (6.0)**	**399 (6.9)**	**246 (5.9)**
Irritability	39 (5.2)	30 (4.0)	255 (5.0)	164 (4.8)	294 (5.0)	194 (4.6)
Personality disorders and disturbance in behaviour	**14 (1.9)**	**12 (1.6)**	**23 (0.5)**	**9 (0.3)**	**37 (0.6)**	**21 (0.5)**
Hostility	8 (1.1)	4 (0.5)	6 (0.1)	1(<0.1)	14 (0.2)	5 (0.1)
Psychiatric and behavioral symptoms NEC	**0**	**0**	**1 (<0.1)**	**2 (0.1)**	**1 (<0.1)**	**2 (<0.1)**
Psychiatric disorders NEC	**5 (0.7)**	**3 (0.4)**	**24 (0.5)**	**19 (0.6)**	**29 (0.5)**	**22 (0.5)**
Schizophrenia and other psychotic disorders	**0**	**0**	**2 (<0.1)**	**1 (<0.1)**	**2 (<0.1)**	**1 (<0.1)**

Sexual dysfunctions, disturbances and gender identity disorders	**2 (0.3)**	**4 (0.5)**	**29 (0.6)**	**17 (0.5)**	**31 (0.5)**	**21 (0.5)**
Sleep disorders and disturbances	**212 (28.2)**	**134 (18.1)**	**1224 (24.1)**	**468 (13.6)**	**1436 (24.7)**	**602 (14.4)**
Abnormal dreams	86 (11.5)	43 (5.8)	494 (9.7)	125 (3.6)	580 (10.0)	168 (4.0)
Initial insomnia	15 (2.0)	9 (1.2)	37 (0.7)	22 (0.6)	52 (0.9)	31 (0.7)
Insomnia	80 (10.7)	51 (6.9)	620 (12.2)	261 (7.6)	700 (12.0)	312 (7.4)
Middle insomnia	17 (2.3)	11 (1.5)	50 (1.0)	15 (0.4)	67 (1.2)	26 (0.6)
Nightmare	13 (1.7)	5 (0.7)	54 (1.1)	22 (0.6)	67 (1.2)	27 (0.6)
Sleep disorder	37 (4.9)	29 (3.9)	173 (3.4)	71 (2.1)	210 (3.6)	100 (2.4)
Somatoform and factitious disorders	**0**	**0**	**0**	**1 (<0.1)**	**0**	**1 (<0.1)**
Suicidal and self-injurious behaviours NEC	**1 (0.1)**	**4 (0.5)**	**9 (0.2)**	**13 (0.4)**	**10 (0.2)**	**17 (0.4)**

Source: Pfizer's ISS Table 23

Events coded to the Psychiatric SOC are presented in the table above. In the RTQ Study, 39.0% of varenicline and 29.0% of placebo subjects had AEs coding to the Psychiatric disorders SOC. These were higher than in the 18-Study cohort (31.8% and 23.4% respectively) and the 19-Study cohort (32.8% and 24.4%, respectively). Psychiatric AEs resulting in permanent discontinuation from study treatment were reported in similar percentages of varenicline and placebo subjects in the RTQ Study (3.2% vs 3.1%, respectively) though higher than in the 18-Study cohort for both treatment groups (2.8% vs 2.5%) and the 19-Study cohort (2.8% vs 2.6%).
In all 3 cohorts, psychiatric events coding to the Sleep disorders and disturbances HLGT were reported by the highest percentage of both varenicline and placebo subjects (RTQ Study: 28.2% varenicline, 18.1% placebo; 18-Study cohort: 24.1% varenicline, 13.6% placebo; 19-Study cohort; 24.7% varenicline, 14.4% placebo). Within that HLGT, the most frequent PTs in all 3 cohorts were Abnormal dreams and Insomnia, which were reported in a higher percentage of varenicline than placebo subjects. For the Sleep disorders and disturbances HLGT overall, as well as the Anxiety disorders and symptoms HLGT and the Depressed mood disorders and disturbances HLGT, the percentage of subjects in both treatment groups was higher in the RTQ Study than in the 18-Study cohort, which Pfizer notes that it may be due to the use of the NAEI in the RTQ study, which was designed to capture psychiatric AEs of interest that were not volunteered spontaneously.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Because the events of interest associated with Chantix tend to be divided among a number of different Preferred Terms (PT), such as depression/depressed mood and anxiety/nervousness, the adverse events reported during the treatment phase were tabulated by High Level Group Term (HLGT) to avoid missing any relevant AEs. The table below, generated from the submitted datasets, shows any HLGT that was reported in at least 5% of the Chantix-treated patients as a treatment-emergent event. Under HLGT, the PTs that were reported in at least 1% of the

Chantix-treated patients are listed. The totals of the PTs may not sum to the total for the HLGT, either because some events were reported in fewer than 1%, or because patients reported more than one PT within the HLGT. Overall, this TEAE profile is similar to the established TEAE profile in prior studies.

Table 23. Common Adverse Events (Source: Reviewer analysis of submitted datasets)

System Organ Class (SOC)	High Level Group Term (HLGT)	Preferred Term (PT)	Varenicline (n,%)		Placebo (n,%)	
Gastrointestinal disorders	*Gastrointestinal motility and defaecation conditions*		72	10	44	6
		Constipation	38	5	13	2
		Diarrhoea	27	4	23	3
		Gastrooesophageal reflux disease	10	1	4	1
	Gastrointestinal signs and symptoms		264	35	117	16
		Abdominal discomfort	7	1	9	1
		Abdominal distention	16	2	8	1
		Abdominal pain	13	2	7	1
		Abdominal pain (upper)	18	2	7	1
		Dyspepsia	20	3	9	1
		Flatulence	17	2	6	1
		Nausea	210	28	67	9
		Vomiting	31	4	13	2
General disorders and administration site conditions	*General system disorders NEC*		120	16	93	13
		Asthenia	12	2	6	1
		Chest pain	8	1	6	1
		Crying	8	1	9	1
		Energy increased	8	1	4	1
		Fatigue	48	6	35	5
		Irritability	39	5	30	4
		Oedema peripheral	4	1	2	0
		Pain	2	0	4	1
		Thirst	5	1	5	1
Infections and infestations	*Infections-pathogen unspecified*		241	32	228	31
		Bronchitis	10	1	23	3
		Cystitis	1	0	4	1
		Ear infection	5	1	3	0
		Gastroenteritis	11	1	8	1
		Gastrointestinal infection	7	1	2	0
		Lower respiratory tract infection	4	1	4	1
		Nasopharyngitis	101	13	94	13

		Otitis externa	5	1	3	0
		Otitis media	6	1	1	0
		Pharyngitis	12	2	8	1
		Respiratory tract infection	4	1	2	0
		Rhinitis	4	1	4	1
		Sinusitis	12	2	16	2
		Tooth abscess	6	1	5	1
		Tooth infection	4	1	4	1
		Upper respiratory tract infection	66	9	64	9
		Urinary tract infection	9	1	7	1
	Viral infectious disorders		40	5	43	6
		Gastroenteristis viral	11	1	8	1
		Influenza	17	2	13	2
		Viral infection	12	2	9	1
		Viral respiratory tract infection	5	1	2	0
Metabolism and nutrition disorders	*Appetite and general nutritional disorders*		62	8	56	8
		Decreased appetite	21	3	21	3
		Hyperphagia	6	1	7	1
		Increased appetite	37	5	30	4
Musculoskeletal and connective tissue disorders	*Musculoskeletal and connective tissue disorders NEC*		53	7	52	7
		Back pain	29	4	29	4
		Musculoskeletal chest pain	4	1	4	1
		Musculoskeletal pain	7	1	3	0
		Neck pain	5	1	8	1
		Pain in extremity	8	1	8	1
Nervous system disorders	*Headaches*		69	9	56	8
		Headache	62	8	54	7
		Migraine	6	1	3	0
	Neurological disorders NEC		79	11	58	8
		Dizziness	32	4	27	4
		Dysgeusia	11	1	10	1
		Hypoaesthesia	1	0	4	1
		Lethargy	9	1	4	1
		Paraesthesia	4	1	4	1
		Somnolence	15	2	10	1
Psychiatric disorders	*Anxiety disorders and symptoms*		83	11	89	12
		Agitation	22	3	15	2
		Anxiety	56	7	69	9
		Nervousness	13	2	11	1
		Panic attack	5	1	3	0
		Stress	3	0	4	1
	Depressed mood disorders		60	8	63	8

	and disturbances					
		Decreased interest	6	1	7	1
		Depressed mood	29	4	28	4
		Depression	25	3	36	5
		Major depression	4	1	0	0
	Sleep disorders and disturbances		215	29	137	18
		Abnormal dreams	86	11	44	6
		Initial insomnia	15	2	10	1
		Insomnia	83	11	51	7
		Middle insomnia	17	2	10	1
		Nightmare	13	2	5	1
		Sleep disorder	37	5	30	4
Respiratory, thoracic and mediastinal disorders	*Respiratory disorders NEC*		48	6	40	5
		Cough	14	2	24	3
		Dyspnoea	5	1	8	1
		Oropharyngeal pain	14	2	6	1
Skin and subcutaneous tissue disorders	*Epidermal and dermal conditions*		36	5	21	3
		Eczema	5	1	5	1
		Pruritis	6	1	4	1
		Rash	9	1	3	0

8.4.6. **Laboratory Findings**

Scheduled central laboratory tests were not performed after screening. Laboratory test abnormalities that were recorded as AEs included blood cholesterol increase for 1 subject in the varenicline treatment group and blood triglycerides increase for 1 subject in the varenicline treatment group; these AEs were considered mild in intensity (Pfizer's table, Section 14.3, table 14.3.1.2.6.

8.4.7. **Vital Signs**

Systolic Blood Pressure (SBP)
Overall, 0.3% and 0.2% of subjects in the varenicline and placebo treatment groups, respectively, had an increase in sitting SBP > 180 mmHg and a change of at least 20 mmHg. A decrease in sitting SBP <90 mmHg and a change of at least 20 mmHg was observed for 0.6% and 0.2% of those in the varenicline and placebo treatment groups, respectively.

Diastolic Blood Pressure (DBP)
Overall, 0.6% and 0.2% of subjects in the varenicline and placebo treatment groups, respectively, had an increase in sitting DBP > 105 mmHg and a change ≥ 15 mmHg. No subjects had significant DBP increases.

Pulse Rate

Overall, 0% and 0.2% of subjects in the varenicline and placebo treatment groups, respectively, had a decrease in sitting PR < 50 beats per minute and a change ≤ 15 beats per minute. No subjects had significant pulse increases.

Table 24.Vital Signs Maximum Change from Baseline, All Treated (Pfizer, Table 14.3.4.2.2)

	Varenicline			Placebo		
Criteria	N	n	%	N	n	%
Sitting Systolic Blood Pressure (mm Hg)						
Increase (BP ≥ 180 and change ≥ 20	687	2	0.3	661	1	0.2
Decrease (BP < 90 and change ≤ 20	687	4	0.6	661	1	0.2
Sitting Diastolic Blood Pressure (mm Hg)						
Increase (BP > 105 and change ≥ 15)	687	4	0.6	661	1	0.2
Decrease (BP < 50 and change ≤ 15)	687	0	0.0	661	0	0.0
Sitting Pulse Rate (bpm)						
Increase (PR > 120 and change ≥ 15)	687	0	0.0	661	0	0.0
Decrease (PR < 50 and change ≤ 15)	687	0	0.0	661	1	0.2

8.4.8. Electrocardiograms (ECGs)

ECGs were performed at screening. According to the study report (table 14.3.4.3), in the All Treated population, ECGs were normal in 79.1 % of subjects randomized to varenicline and 79% randomized to placebo. ECGs had clinically insignificant abnormalities in 20.9 % of subjects randomized to varenicline and 21 % randomized to placebo. On-treatment ECGs were not performed.

8.4.9. QT

No QT abnormalities were reported.

8.4.10. Immunogenicity

Not Applicable

8.5. Analysis of Submission-Specific Safety Issues

The Columbia Suicide Severity Rating Scale (CSSRS) was used in this study to monitor for treatment-emergent suicidality, and the Patient Health Questionnaire (PHQ-9) was used to elicit information about the frequency and severity of events potentially related to depression.

8.5.1. Treatment-Emergent Suicidality and Depression

Columbia-Suicide Severity Rating Scale

The lifetime incidence of suicidal behavior and/or ideation and suicide attempt in the varenicline and placebo treatment groups was 8.7% vs 7.1 % and 2.3% vs 1.9%, respectively. At Baseline, 4 subjects (0.5%) in the placebo group had suicide ideation compared with none (0%) in the varenicline group. During the study, treatment-emergent suicidal behavior and/or ideation was reported for 6 subjects (0.8%) in the varenicline group compared with 10 subjects (1.4%) in the placebo group. Subject (b) (6) in the varenicline group with severe depression and suicidal ideation tried to intentionally injure herself (subject narrative, page 1191 Study Report).

Table 25. Summary of Columbia-Suicide Severity Rating Scale- All Treated Population

Classification Category	Varenicline (N=751)	Placebo (N=742)
Screening (Lifetime)		
Number Assessed	751	742
Suicidal Behavior and/or Ideation	65 (8.7)	53 (7.1)
Suicidal Behavior	20 (2.7)	15 (2.0)
Suicide Attempt	17 (2.3)	14 (1.9)
Preparatory Acts Toward Imminent Suicidal Behavior	9 (1.2)	6 (0.8)
Aborted Attempt	2 (0.3)	3 (0.4)
Interrupted Attempt	5 (0.7)	1 (0.1)
Preparatory Act or Behavior	5 (0.7)	4 (0.5)
Screening (Lifetime)		
Suicide Ideation	58 (7.7)	51 (6.9)
Wish to be Dead	50 (6.7)	39 (5.3)
Non-Specific Active Suicidal Thoughts	28 (3.7)	34 (4.6)
Active Suicidal Ideation with Any Methods (Not Plan) without Intent To Act	11 (1.5)	13 (1.8)
Active Suicidal Ideation with Some Intent To Act without Specific Plan	8 (1.1)	9 (1.2)
Active Suicidal Ideation with Specific Plan and Intent	5 (0.7)	9 (1.2)
Self-Injurious Behavior no Suicidal Intent	8 (1.1)	6 (0.8)

Classification Category	Varenicline (N=751)	Placebo (N=742)
Baseline		
Number Assessed	751	742
Suicidal Behavior and/or Ideation	0	4 (0.5)
Suicidal Behavior	0	0
Suicide Attempt	0	0
Preparatory Acts Toward Imminent Suicidal Behavior	0	0
Aborted Attempt	0	0
Interrupted Attempt	0	0
Preparatory Act or Behavior	0	0
Suicide Ideation	0	4 (0.5)
Wish to be Dead	0	4 (0.5)
Non-Specific Active Suicidal Thoughts	0	1 (0.1)
Active Suicidal Ideation with Any Methods (Not Plan) without Intent To Act	0	1 (0.1)
Active Suicidal Ideation with Some Intent To Act without Specific Plan	0	0
Active Suicidal Ideation with Specific Plan and Intent	0	0
Self-Injurious Behavior no Suicidal Intent	0	0
Treatment-Emergent		
Number Assessed	749	740
Suicidal Behavior and/or Ideation	6 (0.8)	10 (1.4)
Suicidal Behavior	1 (0.1)	0
Completed Suicide	0	0
Suicide Attempt	1 (0.1)	0
Preparatory Acts Toward Imminent Suicidal Behavior	0	0
Aborted Attempt	0	0
Interrupted Attempt	0	0
Preparatory Act or Behavior	0	0
Suicide Ideation	6 (0.8)	10 (1.4)
Wish to be Dead	5 (0.7)	8 (1.1)
Non-Specific Active Suicidal Thoughts	2 (0.3)	6 (0.8)
Active Suicidal Ideation with Any Methods (Not Plan) without Intent To Act	2 (0.3)	2 (0.3)
Active Suicidal Ideation with Some Intent To Act without Specific Plan	0	0
Active Suicidal Ideation with Specific Plan and Intent	1 (0.1)	0
Self-Injurious Behavior no Suicidal Intent	1 (0.1)	0

Classification Category	Varenicline (N=751)	Placebo (N=742)
Follow-up		
Number Assessed	599	564
Suicidal Behavior and/or Ideation	5 (0.8)	3 (0.5)
Suicidal Behavior	1 (0.2)	0
Completed Suicide	0	0
Suicide Attempt	0	0
Preparatory Acts Toward Imminent Suicidal Behavior	1 (0.2)	0
Aborted Attempt	0	0
Interrupted Attempt	0	0
Preparatory Act or Behavior	1 (0.2)	0
Suicide Ideation	5 (0.8)	3 (0.5)
Wish to be Dead	4 (0.7)	3 (0.5)
Non-Specific Active Suicidal Thoughts	4 (0.7)	1 (0.2)
Active Suicidal Ideation with Any Methods (Not Plan) without Intent To Act	3 (0.5)	0
Active Suicidal Ideation with Some Intent To Act without Specific Plan	0	0
Active Suicidal Ideation with Specific Plan and Intent	0	0
Self-Injurious Behavior no Suicidal Intent	0	0

All Treated Population (N) included all subjects who have been randomized and received at least 1 dose, including partial doses, of randomized study medication.
Source: Section 14.3, Table 14.3.4.1

Patient Health questionnaire (PHQ-9)

At Baseline, the majority of subjects in the varenicline group and in the placebo group were categorized as none (0-4) for severity of depression (634 [84.5%] vs 635 [85.7%]). The percentage of subjects in the varenicline and placebo groups with mild (5-9), moderate (10-14), moderately severe (15-19), and severe depression (20-27) at Baseline was 12.7% vs 10.8%, 2.1% vs 3.1%, 0.7% vs 0.3%, and 0% vs 0.1%, respectively.

Tables 26 and 27 below show the shift in depression severity category from baseline PHQ-9 score to worst post-baseline for up to 30 days. The percentage of PHQ-9 scores worsening while on study drug in the varenicline group and the placebo group were 22.5% vs 19.5% respectively. The majority of worst post-baseline assessments were mild 14.4% vs 13.1%, and moderate 5.4% vs. 4.1%. Few worst post-baseline assessments were moderately severe 1.6% vs 1.5% and severe 1.1% vs 0.9%. Overall, both treatment groups were similar in worsening depression category post-baseline.

Table 26. PHQ-9 Shift in Depression Category from baseline to worst post-baseline (30 days)-All-Treated Population, Varenicline Arm (N=751)

	Worst Post-Baseline Assessment				
Baseline (N= 741)	None n(%)	Mild n(%)	Moderate n(%)	Moderately severe n(%)	Severe n(%)
None	480 (63.9)	108 (14.4)	28 (3.7)	8 (1.1)	5 (0.7)
Mild	36 (4.8)	38 (5.1)	13 (1.7)	3 (0.4)	2 (0.3)
Moderate	3 (0.4)	9 (1.2)	2 (0.3)	1 (0.1)	0 (0.0)
Moderately Severe	1 (0.1)	2 (0.3)	1 (0.1)	0 (0.0)	1 (0.1)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Notes: All Subjects population is defined as all subjects who have received at least one dose of Study Drug. N= Number of subjects with a baseline PHQ-9 assessment and at least one post-baseline assessment done. Percentages are in reference to treatment group total.
None= 0-4
Mild= 5-9
Moderate= 10-14
Moderately Severe= 15-19
Severe= 20-27
When there were multiple post-baseline assessments within the same week, the one with the highest score was used.

Table 27. PHQ-9 Shift in Depression Category from baseline to worse post-baseline (30 days) All-Treated Population, Placebo Arm (N=742)

	Worst Post-Baseline Assessment				
Baseline (N= 730)	None n(%)	Mild n(%)	Moderate n(%)	Moderately severe n(%)	Severe n(%)
None	504 (67.9)	97 (13.1)	16 (2.2)	5 (0.7)	4 (0.5)
Mild	26 (3.5)	34 (4.6)	14 (1.9)	4 (0.5)	1 (0.1)
Moderate	3 (0.4)	8 (1.1)	7 (0.9)	2 (0.3)	2 (0.3)
Moderately Severe	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)
Severe	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)

Notes: All Subjects population is defined as all subjects who have received at least one dose of Study Drug. N= Number of subjects with a baseline PHQ-9 assessment and at least one post-baseline assessment done. Percentages are in reference to treatment group total.
None= 0-4
Mild= 5-9
Moderate= 10-14
Moderately Severe= 15-19
Severe= 20-27
When there were multiple post-baseline assessments within the same week, the one with the highest score was used.

8.6. Specific Safety Studies/Clinical Trials

Not Applicable

8.7. Additional Safety Explorations

Sub-sections deleted, not applicable.

8.8. Safety in the Postmarket Setting

8.8.1. Safety Concerns Identified Through Postmarket Experience

A summary of post-marketing experience was submitted as part of the Integrated Summary of Safety. The cumulative review of postmarketing cases through 31 December 2014 (excluding Pfizer-sponsored interventional clinical trial cases) did not identify any new safety concerns.

Two new post-market safety issues have been reviewed by DPV since the last label change, somnambulism and glycemic disorders.

Somnambulism

DPV reviewed 61 FAERS cases of somnambulism with harmful behavior associated with varenicline in December, 2015. In most cases, somnambulism resulted in actual or potential harm or injury to a person (and a few to only property). In most cases, the harmful activity occurred outside of the patient's bed and a few occurred within the bed; amnesia was present in 18 of the 61 cases. The most common harmful incidences (decreasing rank) were falls, assaults, automobile operation, and starting fire and getting burned. About half of the cases also reported abnormal dreams or nightmares (both labeled). Positive dechallenge and event onset time (median 3 weeks) support a causal role for varenicline. Varenicline was likely the sole contributor to the somnambulism and harmful behavior in three cases because confounding factors (prior somnambulism occurrence, psychiatric history or concurrent psychotherapeutics and concomitant alcohol) were absent. DPV recommends adding the following information to the WARNINGS AND PRECAUTIONS section (within serious neuropsychiatric events): *Cases of somnambulism resulting in harmful behavior to self, others and property have been associated with varenicline treatment.* DPV also recommended that this somnambulism information should also be briefly mentioned in BOXED WARNING for serious neuropsychiatric events; however, the boxed warning is currently being reevaluated in the context of the results of the NPS study.

Glycemic Disorders

DPV reviewed 186 FAERS reports in January, 2016, and identified 39 cases of hyperglycemia/diabetes (n=27), and hypoglycemia (n=12) that were temporally associated with varenicline therapy. The FAERS cases and known pharmacologic activity of varenicline provide some support for a possible association between varenicline and hyperglycemia, diabetes mellitus, and hypoglycemia. Diabetes mellitus and hypoglycemia are already listed as adverse events in product labeling, and it is reasonable to also include hyperglycemia. However, due to the high background rate of diabetes in the general population as well as possible confounding by drug metabolism changes, underlying or unrecognized diabetes, and changes in diet, it is difficult to confidently assert there is a compelling safety signal.

8.8.2. Expectations on Safety in the Postmarket Setting

As noted above, no new safety concerns were identified by the Sponsor.

8.9. Additional Safety Issues From Other Disciplines

No other safety issues noted.

9 Advisory Committee Meeting and Other External Consultations

No Advisory Committee is planned for this Submission.

10 Labeling Recommendations

10.1. Prescribing Information

The currently approved version of the Chantix US Package Insert (USPI) is LAB-0327-20.0, dated October 2014. The current submission supports proposed changes to the USPI based on the outcomes of this "Reduce-to-Quit" study (A3051075) and proposed changes to the USPI consistent with the requirements under the FDA Pregnancy and Lactation Labeling Rule (PLLR). The following are Pfizer's proposed changes to each label section followed by reviewer comments.

Section 2. Dosage and Administration

- To the highlight section: "Consider a gradual approach to quitting smoking with CHANTIX for patients who are not able or willing to quit abruptly. Patients should begin CHANTIX dosing and reduce smoking [redacted] (b) (4) continue treatment for an additional 12 weeks for a total of 24 weeks. (2.1)"
- To the full prescribing information: [redacted] (b) (4)

Reviewer comment: *Change* [redacted] (b) (4)

Section 5. Warnings and Precautions

- No changes submitted from Pfizer except minor revisions, such as (b) (4)

Reviewer comment: *In the highlight section, the review team proposed to add to the Recent Major Changes, "Warnings and Precautions, Somnambulism (5.6), and remove all the prior major changes dated 9/2014. Add text, "Somnambulism: Cases of somnambulism resulting in harmful behavior to self, others and property have been associated with varenicline treatment. Instruct patients to discontinue CHANTIX and notify their healthcare provider if they experience these symptoms."*

Section 6.1. Clinical Trials Experience

- Addition of study A3051075,.." a trial in patients who were not able or willing to quit abruptly and who were instructed to quit gradually (gradual approach to quitting smoking trial)," noting that the adverse events were similar to those observed in postmarketing studies.

Reviewer comment: *The review team agreed with this change.*

Section 6.2. Postmarketing Experience

- No changes were submitted by Pfizer to this section.

Reviewer comment: *The review team proposed the following addition: "There have been reports of somnambulism resulting in harmful behavior to self, others and property have been associated with varenicline treatment [see Warnings and Precautions (5.6)].*
There have been reports of hyperglycemia in association with CHANTIX treatment.

Section 8.1 Pregnancy

- To the full prescribing information: Remove pregnancy category C, and first paragraph. Replace the text with:

"Risk Summary: (b) (4)

Clinical Considerations: Disease-associated maternal and/or embryo/fetal risk: (b) (4)

- To the full prescribing section: (b) (4) "Lactation." Add to the Data section, "In a pre- and postnatal development study, pregnant rats received up to 15 mg/kg/day of oral varenicline succinate through gestation and lactation (b) (4) mean serum concentrations in the nursing pups were 5-22% of maternal serum concentrations."

Reviewer comment: *Based on input from the Maternal Health Team, the review team proposed the following:*

<u>Risk Summary:</u> Available human data on the use of CHANTIX in pregnant women are not sufficient to inform a drug associated risk. Smoking during pregnancy is associated with maternal, fetal, and neonatal risks [see Clinical Considerations]. In animal studies, varenicline did not result in major malformations but caused decreased fetal weights in rabbits when dosed during organogenesis at exposures equivalent to 50 times the exposure at the maximum recommended human dose (MRHD). Additionally, administration of varenicline to pregnant rats during organogenesis through lactation produced developmental toxicity in offspring at maternal exposures equivalent to 36 times human exposure at the MRHD [see Data]. The background risk of major birth defects and miscarriage for the indicated population are unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20, respectively.

<u>Clinical Considerations</u>: Disease-associated maternal and/or embryo/fetal risk:
Smoking during pregnancy causes increased risks of premature rupture of membranes, placenta previa, placental abruption, ectopic pregnancy, fetal growth restriction and low birth weight, stillbirth, preterm delivery and shortened gestation, neonatal death, sudden infant death syndrome and reduction of lung function in infants.
<u>Data- Animal Data</u>
Pregnant rats and rabbits received varenicline succinate during organogenesis at oral doses up to 15 and 30 mg/kg/day, respectively. While no fetal structural abnormalities occurred in either species, maternal toxicity characterized by reduced body weight gain as well as reduced fetal weights occurred in rabbits at the highest dose (exposures 50 times the human exposure at the MRHD of 1 mg twice daily based on AUC). Fetal weight reduction did not occur in rabbits at exposures 23 times the human exposure at the MRHD based on AUC. In a pre- and postnatal development study, pregnant rats received up to 15 mg/kg/day of oral varenicline succinate from organogenesis through lactation. Maternal toxicity, characterized by a decrease in body weight gain was observed at 15 mg/kg/day (36 times the human exposure at the MRHD based on AUC). However, decreased fertility and increased auditory startle response occurred in offspring at the

highest maternal dose of 15 mg/kg/day.

Section 8.2. Lactation

- To the highlight section: [redacted] "Lactation.

Reviewer Comment: *Revise the section to read as follows:*

Risk Summary

There are no data on the presence of varenicline in human milk, the effects on the breastfed infant, or the effects on milk production. In animal studies varenicline was present in milk of lactating rats [see Data]. However, due to species-specific differences in lactation physiology, animal data may not reliably predict drug levels in human milk. [redacted]

Clinical Considerations

[redacted].

Data

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

Section 14. Clinical Studies

- Modify second paragraph to read, "Six additional studies were conducted in patients with cardiovascular disease, in patients with chronic obstructive pulmonary disease [see Clinical Studies (14.[redacted])], and in patients instructed to select their quit date within days 8 and 35 of treatment [see Clinical Studies (14[redacted]], patients with major depressive disorder [(see Clinical Studies (14.8)], patients who had made a previous attempt to quit smoking with CHANTIX, and either did not succeed in quitting or relapsed after treatment [see Clinical Studies (14.6)], and in patients who were not able or willing to quit abruptly and were instructed to quit gradually [see Clinical studies (14.5])."
- [redacted].

Reviewer comment: *The review team agrees with Pfizer's changes,* [redacted]

(b) (4)

Section 17. Patient Counseling Information

- (b) (4)

[see Dosage and Administration (2.1)]."

Reviewer comment: (b) (4)

10.2. Patient Labeling

Medication Guide.

Pfizer proposed the following changes to the section, "How should I take CHANTIX?":

- Modify the language to read, "There are 3 ways that you can use CHANTIX to help you quit smoking. Talk to your doctor about the following 3 ways to use CHANTIX:
  Choose a quit date when you will stop smoking. Start taking CHANTIX 1 week (7 days) before your quit date. Take CHANTIX for 12 weeks.
  OR
  Start taking CHANTIX before you choose a quit date. Pick a date to quit smoking that is between days 8 and 35 of treatment. Take CHANTIX for 12 weeks.
  OR
  If you are not able or willing to quit smoking right away, start taking CHANTIX and reduce smoking during the first 12 weeks of treatment, and then quit by the end of that treatment period. You should then continue to take CHANTIX for another 12 weeks, resulting in a total of 24 weeks of treatment."

Reviewer comment: *The review team agrees with the above text from Pfizer. In addition, the review team proposed the additional language, "If you are breastfeeding, you should monitor your baby for seizures and vomiting," to the section, "What is important information I should know about CHANTIX? (last paragraph)."*

10.3. Nonprescription Labeling

Not applicable.

11 Risk Evaluation and Mitigation Strategies (REMS)

The REMS for this product is a medication guide. The medication guide should be revised to include new dosing recommendations.

11.1. Safety Issue(s) that Warrant Consideration of a REMS

No new safety issues were identified in this review than warrant further REMS consideration.

11.2. Conditions of Use to Address Safety Issue(s)

Not applicable.

11.3. Recommendations on REMS

Revise the dosing instructions in the medication guide to reflect gradual reduction to quit indication.

12 Postmarketing Requirements and Commitments

No additional postmarketing requirements are recommended at this time.

13 Appendices

13.1. References

Lindson-Hawley, N. B. (2016). Gradual Versus Abrupt Smoking Cessation: A Randomized, Controlled Noninferiority Trial. *Annals of Internal Medicine*.

13.2. Financial Disclosure

A Form FDA 3455, Disclosure Statement was provided for each clinical investigator who, or whose spouse or dependent child, had disclosable financial interests in and/or arrangements with any sponsor of the covered clinical study. Five of the 215 clinical investigators listed in the study report had financial information to disclose. See section 6.1.1.

Clinical Review
Sarah Arnold, M.D., M.P.H.
NDA Supplement 039
Chantix (varenicline)

A Phase 4, Multi-National, Randomized, Double-Blind, Placebo Controlled Study to Evaluate the Efficacy and Safety of Varenicline Compared to Placebo for Smoking Cessation Through Reduction: A3051075

Was a list of clinical investigators provided:	Yes X	No ☐ (Request list from Applicant)
Total number of investigators identified: 215		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 5		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 5 Significant payments of other sorts: 5 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Study: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes X	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes X	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes X	No ☐ (Request explanation from Applicant)

Clinical Review
Sarah Arnold, M.D., M.P.H.
NDA Supplement 039
Chantix (varenicline)

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

/s/

SARAH J ARNOLD
06/08/2016
Clinical Review of S039

CELIA J WINCHELL
06/08/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021928/S-039

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF ANESTHESIA, ANALGESIA, AND ADDICTION PRODUCTS

PHARMACOLOGY/TOXICOLOGY REVIEW – MEMO TO FILE

NDA Number:	21928
Supporting Document Number:	SDN 39
Submit Date / Received Date:	10-13-15 / 10-13-15
Type of Submission:	NDA Efficacy Supplement
Sponsor:	Pfizer, Inc. 235 East 42nd Street MS 605 6 31 New York, New York 10017
Reviewer Name:	Kevin Snyder, PhD
Team Leader:	Newton Woo, PhD
Supervisor:	R. Daniel Mellon, PhD
Division Name:	Division of Anesthesia, Analgesia, and Addiction Products
HFD #:	170
Date of Memo:	June 8, 2016
Drug:	CHANTIX (varenicline)
Indication:	Aid to smoking cessation.

Recommendation: Labeling was updated to reflect PLLR format. The Sponsor's proposed labeling changes are acceptable from the nonclinical perspective with the recommended modifications listed below.

Background/Prior Regulatory History

CHANTIX (varenicline tartrate) was approved on May 10th, 2006. An efficacy supplement, entitled "Clinical Data on Smoking Cessation Through Reduction", was submitted on October 13th, 2015. Although no new nonclinical data was included in this supplement, it did contain updated labeling in compliance with the Pregnancy and Lactation Labeling Rule (PLLR). Sections 8 and 13 of the proposed labeling changes were reviewed and modified to reflect proper PLLR conversion from the nonclinical perspective.

The following changes to the Applicant's proposed labeling are recommended in the table below. Refer to the action letter for final drug product labeling. Recommended additions are noted in red text whereas deletions are noted in crossed out text.

(b) (4)

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

---

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

/s/

KEVIN P SNYDER
06/08/2016

NEWTON H WOO
06/08/2016
I concur.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021928/S-039

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

NDA/BLA Serial Number:	NDA 21928 / S-039
Drug Name:	Chantix (varenicline)
Indication(s):	Smoking Cessation for Smokers on Reduce-to-Quit schedule
Applicant:	Pfizer, Inc.
Date(s):	Submission Stamp Date: October 13, 2015 PDUFA Date: August 13, 2016 Primary Review Completion Due Date: June 8, 2016
Review Priority:	Standard
Biometrics Division:	Division of Biometrics 2
Statistical Reviewer:	Kate Meaker, M.S.
Concurring Reviewers:	David Petullo, M.S. - Team Leader
Medical Division:	Division of Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Clinical Team:	Sarah Arnold, M.D. – Clinical Reviewer Celia Winchell, M.D. – Clinical Team Leader
Project Manager:	Ayanna Augustus, Ph.D.

Keywords: clinical studies

Table of Contents

1. EXECUTIVE SUMMARY

Chantix (varenicline) is currently approved as an aid to smoking cessation treatment. Based on the results from a phase 4 study that evaluated a 'reduce to quit' approach for smoking cessation, the applicant requests that the Dos(b) (4) and Administration section of the label be revised to include the following instructions:

> Consider a gradual approach to quitting smoking with CHANTIX for patients who are (b) (4)

In this phase 4 study smokers agreed to follow a prespecified plan to reduce the number of cigarettes smoked over the first 12 weeks of treatment, with the intent to quit fully by Week 12.

Study A3051075 (Study 1075) was a randomized, double-blind, multicenter study comparing varenicline to placebo in adults trying to quit smoking. The study design, dosing regimen, efficacy endpoints, and analyses were mostly similar to the Phase 3 studies used to support the initial application in 2005. They main difference was in the timing and manner of the attempt to quit smoking. During the first 4 weeks of treatment subjects agreed to reduce the number of cigarettes smoked by at least 50% from baseline; by 8 weeks they would reduce by 50% again (75% from baseline); and at Week 12 the intent was to quit entirely. Treatment with study drug continued through Week 24.

Efficacy was assessed using a Nicotine Use Inventory and end-expiratory exhaled carbon monoxide (exhaled CO) monitoring. The primary and key secondary endpoints were defined based on those measures. The primary endpoint was the 9-week continuous abstinence rate (CAR) from weeks 15-24, which was compiled from reported cigarette or other nicotine product use, along with confirmed exhaled CO $\leq$ 10 ppm. Two secondary endpoints (CAR at weeks 21-24 and CAR at weeks 21-52) were predefined with the intended goal of inclusion of the results in the label. Weeks 21-24 correspond to the last 4 weeks of treatment. Weeks 21-52 are represent long-term abstinence. Other endpoints were considered exploratory only.

The efficacy endpoints were tested using a logistic regression model with terms for treatment group and pooled center. In order to preserve the Type I family-wise error rate of 0.05, a hierarchical closed testing procedure was used for the analysis of the primary and secondary endpoints. The order of testing was 1) the CAR for weeks 15-24; and 2) CAR for weeks 21-24; and 3) CAR for weeks 21-52. Each comparison was tested at α=0.05.

On all three endpoints, the varenicline treatment group was statistically significantly better than the placebo treatment group ($p<0.001$). The results, which are presented in Table 3, provide sufficient evidence to support the efficacy of varenicline as an aid to smoking cessation for smokers who are not willing to quit abruptly but who are willing to reduce smoking over the first 12 weeks of treatment to achieve abstinence by the 12th week of treatment.

Based on my evaluation of the study, I conclude that there is evidence that varenicline is an effective aid to smoking cessation in patients who are not willing or able to quit abruptly but who are willing to follow the reduction plan proposed in this study.

2. INTRODUCTION

2.1 Overview

Chantix, a nicotinic receptor partial agonist was approved in 2006 as an aid to smoking cessation treatment. The current label includes instructions for the patient to select a target quit date and then start treatment with varenicline one week prior to that target quit date.

In the current submission, for patients who are not able to or are unwilling to quit abruptly, the applicant proposes a reduce to quit approach. To support this approach, the applicant submitted the results from a single randomized, double-blind, placebo-controlled study, A3051075 (1075). In this study, smokers agreed to reduce the number of cigarettes smoked by 50% after 4 weeks of treatment, by an additional 50% after 8 weeks of treatment, and to completely quit by Week 12 of treatment. The protocol for Study 1075 was discussed in advice letters in April and November, 2010 (IND 58994). Topics included timeframes and secondary endpoints and were addressed in protocol revisions.

2.2 Data Sources

The full submission was organized in electronic common technical document DTD version 3.2. All data was supplied by the applicant to the CDER electronic data room (edr) in SAS transport format. All necessary documentation, formats, and links were provided as well. The data and final study report for the electronic submission were archived under the network path locations: \\Cdsesub1\evsprod\NDA021928\0347 and \\Cdsesub1\evsprod\NDA021928\0365. The latter includes data sets submitted in response to an Information Request letter dated March 23, 2016.

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The applicant provided data sufficient to confirm all relevant results from the study report. The tables were clearly identified, and links to supporting output or information in the Appendices was provided.

3.2 Evaluation of Efficacy

Study Design and Endpoints

Study 1075 was a 24-week, randomized, double-blind, placebo-controlled study that was conducted in 61 centers in the United States, Canada, Mexico, Europe, Egypt, Japan, Taiwan, and Australia from 2011-2013. This study enrolled adult patients that were current smokers (at least 10 cigarettes per day during the previous 4 weeks) with no continuous period of abstinence greater than 3 months in the past year. These patients were not willing to stop smoking abruptly within the next month but were willing to attempt to quit by following the reduce to quit approach within the next 3 months. Patients with a history of lifetime or current mild to moderate (investigator opinion) major depressive disorder (MDD), depression, depressed mood, anxiety, and anxiety disorders (including generalized anxiety disorder [GAD], obsessive compulsive disorder [OCD] and phobias such as agoraphobia and social phobia) were permitted to be included if their condition was stable. Subjects with a history of a suicide attempt or any suicidal behavior, major depression, or a diagnosis or treatment for psychosis, panic disorder, bipolar disorder, posttraumatic stress disorder, or schizophrenia were excluded.

Subjects were randomized to either Chantix 1 mg twice daily or placebo for 24 weeks and followed up for post-treatment through week 52. Subjects were instructed to reduce the number of cigarettes smoked by at least 50 percent by the end of the first four weeks of treatment, followed by a further 50 percent reduction from week four to week eight of treatment, with the goal of reaching complete abstinence by 12 weeks. After the initial 12-week reduction phase, subjects continued treatment for another 12 weeks. Use of nicotine replacement therapy or other nicotine-containing products was prohibited during the study.

Clinic visits were scheduled at Week 1, 2, 4, 6, 8, 12, 15, 18, 21, 22, 23, and 24 during the 24-week treatment period, and at Weeks 26, 32, 40, 48 and 52 during the post-treatment period. Phone contact was scheduled at Weeks 3, 5, 7, 10, 14, 16, 20, 28, 36 and 44. Use of cigarettes or other nicotine-containing products was measured using the Nicotine Use Inventory (NUI) at all clinic visits or phone contacts throughout the 52 week study. Exhaled carbon monoxide (CO) was measured at each clinic visit.

The primary and secondary endpoints were defined based on the NUI and exhaled CO measures. The primary endpoint was the continuous abstinence rate (CAR) from Weeks 15-24, which was compiled from reported cigarette or other nicotine product use, along with confirmed exhaled CO $\leq$ 10 ppm. The results for two secondary endpoints, continuous abstinence rate (CAR) from Weeks 21-24 (last 4 weeks of treatment) and CAR from Weeks 21-52 (long term abstinence) were included in section 14 of the product label. Other secondary endpoints were considered exploratory only.

If a CO measurement at a particular timepoint was > 10 ppm then the subject was considered a smoker at that timepoint. Missed exhaled CO measurements were imputed as negative "therefore not disqualifying the subject as a responder" according to the statistical analysis plan (section 6.1.1). In my review, I checked how many subjects classified as responders for continuous abstinence had missing CO measurements. For the primary endpoint (weeks 15-24),

there were 29 who were missing one or more of the CO assessments scheduled for weeks 15, 18, 21, 22, 23, or 24. Of them, only one, in the Varenicline group, did not have a confirming CO through Week 24, but did have confirming NUI data recorded for all the weeks in that interval. For the long-term abstinence endpoint (weeks 21-52), 36 subjects were missing one or more CO values scheduled during that timeframes, but all had confirmatory CO assessments after the missing one timepoints. The imputation of the missing CO measurements did not impact the results.

For the Nicotine Use component, the wording on the NUI questionnaire asks about use since last contact, so any missed measurements were to be imputed based on the current response. Any subjects who discontinued from the study were coded as smokers (non-responders) from the time of discontinuation through the end of the study. Subjects were allowed to discontinue treatment but continue in the study, in which case the efficacy outcomes were determined by observed data.

For the efficacy endpoints, the primary analyses used the Full Analysis Set (FAS), also known as the Intent-to-Treat (ITT) population, defined as all randomized patients.

Patient Disposition, Demographic and Baseline Characteristics

A total of 1510 subjects were randomized and received study treatment. There were 17 subjects randomized but did not receive study treatment. In the SAS datasets, the reasons for these subjects not receiving treatment were primarily no longer willing to participate or lost-to-follow-up.

As shown in Table 1, a higher percentage of subjects discontinued from the placebo arm than the varenicline treatment arm, primarily due to a higher incidence of subjects reporting lack of efficacy in the placebo arm during the treatment phases (weeks 1-24).

Table 1: Patient Disposition (Study 1075)

	Varenicline	Placebo
Randomized (FAS)	760 (100%)	750 (100%)
Received Study Treatment	751 (99%)	742 (99%)
Discontinued During Treatment/Reduce-to-Quit Phase (Weeks 1-12)	103 (14%)	131 (17%)
Reason for Discontinuation:		
Adverse Event	9 (1)	10 (1)
Lack of Efficacy	6 (1)	17 (2)
Lost to Follow-up	37 (5)	45 (6)
Subject no longer willing to participate	29 (4)	32 (4)
Other	22 (3)	27 (4)
Discontinued During Treatment/Abstinence Phase (Weeks 13-24)	38 (5%)	52 (7%)
Reason for Discontinuation:		
Adverse Event	3 (<1)	2 (<1)
Lack of Efficacy	0 (0)	10 (1)
Lost to Follow-up	17 (2)	20 (3)
Subject no longer willing to participate	13 (2)	14 (2)
Other	5 (1)	6 (1)
Discontinued During Post-treatment Phase (Weeks 25-52)	51 (7%)	44 (6%)
Reason for Discontinuation:		
Adverse Event	1 (<1)	1 (<1)
Lack of Efficacy	0 (0)	1 (<1)
Lost to Follow-up	22 (3)	16 (2)
Subject no longer willing to participate	12 (2)	13 (2)
Other	16 (2)	13 (2)
Completed Treatment	564 (74%)	513 (68%)
Completed Study	559 (74%)	516 (69%)

Source: Modified from Clinical Study Report Table 9
All percentages are calculated based on Randomized N per group as denominator.

Baseline Demographics

The two treatment groups were well balanced with respect to relevant demographic and baseline characteristics as shown in Table 2.

Table 2: Demographic Characteristics

All Randomized	**Varenicline N=760**	**Placebo N=750**
Age (years)		
Mean (SD)	45 (12)	44 (12)
Range	19 – 79	18 – 78
Age group:		
≤65 yrs	725 (95%)	708 (94%)
>65 yrs	35 (5%)	42 (6%)
Gender		
Female	335 (44%)	324 (43%)
Male	425 (56%)	426 (57%)
Race		
Caucasian	476 (63%)	463 (62%)
Black	36 (5%)	47 (6%)
Asian	175 (23%)	177 (24%)
Other	73 (10%)	63 (8%)
Region		
North America (US; Can.; Mex.)	341 (45%)	336 (45%)
Europe (UK; Germ.; Czech Rep)	203 (27%)	203 (27%)
Asia/Pacific (Australia; Japan; Taiwan; Egypt)	216 (28%)	211 (28%)
Number of Cigarettes Smoked per Day at Baseline		
Mean (SD)	20 (8)	20 (8)
Range	2 – 70	2 – 60

Sources: Reviewer

Statistical Methodologies

The primary and secondary efficacy endpoints (CAR at weeks 15-24, 21-24, and 21-52) were tested using a logistic regression model with terms for treatment group and center. In order to preserve the Type I family-wise error rate of 0.05, a fixed-sequence hierarchical closed testing procedure was utilized. The order of testing was 1) the CAR for weeks 15-24; 2) CAR for weeks 21-24; and 3) CAR for weeks 21-52. Each comparison was tested at α=0.05.

Results and Conclusions

On both the primary and secondary efficacy endpoints, the varenicline treatment group was statistically significantly better than the placebo treatment group ($p<0.001$). Table 3 presents the applicant's results, along with additional endpoints of interest to the clinical reviewer, Dr. Arnold. The applicant's analyses were conducted as planned in the protocol and I was able to replicate the applicant's results.

Table 3: Efficacy Analysis Results

All Subjects	Varenicline	Placebo	Odds Ratio (95% CI)	p-value
Primary:				
Continuous Abstinence Rate Weeks 15-24	244/760 32%	52/750 7%	8.7 (6.1, 12.5)	p<0.001 [a]
Continuous Abstinence Rate Weeks 15-52	182/760 24%	45/750 6%		
Secondary:				
Continuous Abstinence Rate Weeks 21-24	287/760 38%	94/750 13%	5.7 (4.2, 7.6)	p<0.001 [a]
Secondary:				
Continuous Abstinence Rate Weeks 21-52	205/760 27%	74/750 10%	4.0 (2.9, 5.5)	p<0.001 [a]
Reduce by 50% from Baseline to Week 4	485/760 64%	278/750 37%		
Reduce by 75% from Baseline to Week 8	450/760 59%	225/750 30%		
Reduce by 100% from Baseline to Week 12 (Quit by Week 12)	224/760 29%	48/750 6%		

Source: Modified from Clinical Study Report Table 15

[a] The odds ratios and p-values were obtained from a logistic regression model including the main effects of treatment and pooled center.

Since the clinical review team noted an excessive amount of financial compensation to the investigators at five sites (1024, 1035, 1039, 1067, and 1077) additional analyses were conducted excluding the data from these sites. These sites enrolled a total of 125 subjects (62 in varenicline; 63 in placebo). The results are shown in Table 4. Excluding the data from these sites did not change the conclusions. There were more subjects randomized to Chantix that were able to stop smoking when compared to placebo.

Table 4: Efficacy Analysis Results – Exclude Sites 1024, 1035, 1039, 1067, 1077

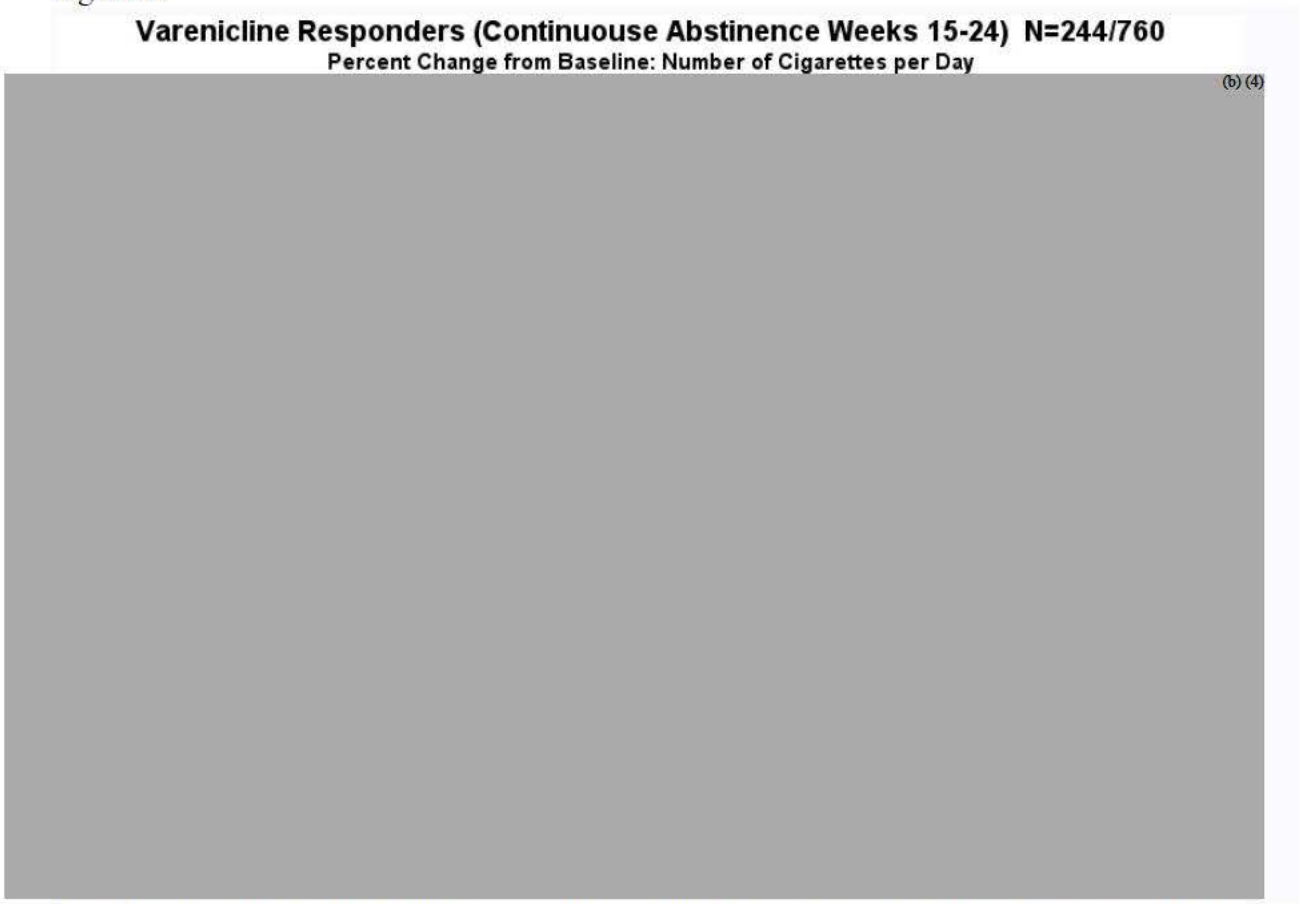
	Varenicline	Placebo	Odds Ratio (95% CI)	p-value
Continuous Abstinence Rate Weeks 15-24	222/698 32%	51/687 7%	8.0 (5.5, 11.6)	p<0.001 [a]
Continuous Abstinence Rate Weeks 15-52	163/698 23%	45/687 7%		
Continuous Abstinence Rate Weeks 21-24	262/698 38%	92/687 13%	5.2 (3.8, 7.0)	p<0.001 [a]
Continuous Abstinence Rate Weeks 21-52	185/698 27%	74/687 11%	3.5 (2.6, 4.8)	p<0.001 [a]
Reduce by 50% from Baseline to Week 4	437/698 63%	257/687 37%		
Reduce by 75% from Baseline to Week 8	409/698 59%	211/687 31%		
Reduce by 100% from Baseline to Week 12 (Quit by Week 12)	201/698 29%	47/687 7%		

Source: Reviewer

[a] The odds ratios and p-values were obtained from a logistic regression model including the main effects of treatment and pooled center.

The clinical review team also questioned whether the subjects that did stop smoking were following the reduce-to-quit schedule as planned in the protocol. I produced the plots in Figures 1 and 2 for the smokers who were responders for the primary efficacy endpoint: continuous abstinence from week 15 through 24. There are 244 responders in the varenicline group, and 52 in the placebo group. Comparing the two plots suggests those in the varenicline were better able to follow the gradual reduce-to-quit schedule.

Figure 1:

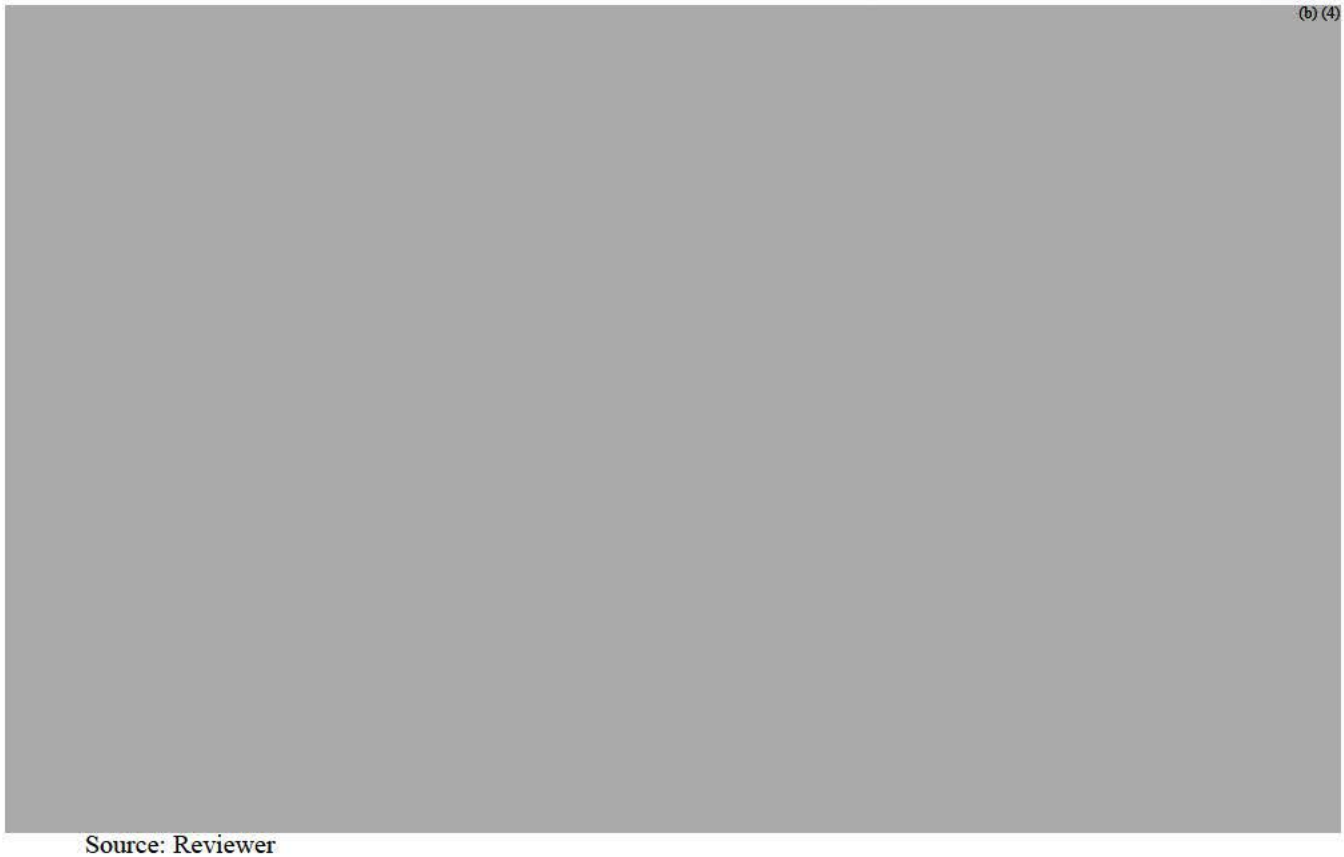


Note: The colored dots and letter markings are due to multiple observations with similar values among the 244 individual records represented on the single plot.
Source: Reviewer

Figure 2:

Placebo Responders (Continuouse Abstinence Weeks 15-24) N=52/750

Percent Change from Baseline: Number of Cigarettes per Day



Source: Reviewer

The clinical team is interested in comparing the subsets of smokers who were able to quit by Week 4 of this study, i.e. did not need to follow the reduce to quit plan, to the smokers who quit be Week 12 as planned. I divided the subjects into three subgroups based on smoking status at Week 4 and Week 12. Subjects who did not smoke during Week 4 but did smoke during later weeks were still classified as CO-confirmed Quit at Week 4. Table 5 shows the results for these three subsets, which indicate that continuous abstinence rates were similar for smokers who quit by Week 4 or Week 12 in the population of smokers not willing to try to quit abruptly.

Table 5: Smokers Who Quit by Week 4 or by Week 12 – Reviewer's Results

Subgroup	Continuous Abstinence Rate		
	Varenicline (N=760)	Placebo (N=750)	Difference
CO-Confirmed Quit at Week 4			
Responder at Weeks 15-24	47/64 (73%)	2/4 (50%)	23%
Responder at Weeks 21-52	42/64 (66%)	2/4 (50%)	16%
CO-Confirmed Quit at Week 12 (but not at Week 4)			
Responder at Weeks 15-24	145/167 (87%)	28/44 (64%)	23%
Responder at Weeks 21-52	111/167 (66%)	29/44 (66%)	0%
Not CO-Confirmed Responder at Week 4 or Week 12			
Responder at Weeks 15-24	52/529 (10%)	22/702 (3%)	7%
Responder at Weeks 21-52	52/529 (10%)	43/702 (6%)	4%

Source: Reviewer

Lastly, I compared the proportion of all randomized subjects who were responders for short-term efficacy (Continuous Abstinence for Weeks 15 through 24) but did not quit by Week 4. In the varenicline group there were 197/760 (26%) who met this criterion, and in the placebo group there were 50/750 (7%) who did. The difference between the groups is 19% (95%CI: 16%, 23%).

Study 1075 provides sufficient evidence to support the inclusion of these results in the Clinical Studies section of the label as an aid to smoking cessation in subjects who follow the reduce-to-quit schedule used in this study.

3.3 Evaluation of Safety

Dr. Arnold completed the safety review for this study. She did not request any additional safety analyses.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

I reviewed exploratory analyses for the primary endpoint by age groups, sex, race, and region (See Table 6). The only notable difference in the subgroup tables is that both treatment arms had lower responder rates in North America than in Europe or the Asia/Pacific region. In each region, the varenicline group had a higher rate of success than the placebo group.

These are descriptive analyses only and are not intended for inferential purposes. The varenicline treatment group consistently showed a higher continuous abstinence rate than the placebo group.

Table 6: Subgroup Analyses: Age, Gender, Race and Region – Reviewer's Results

Subgroup	Continuous Abstinence Rate Weeks 15-24	
	Varenicline (N=760)	Placebo (N=750)
Age group		
≤ 65 years	232/725 (32%)	48/708 (7%)
> 65 years	12/35 (34%)	4/42 (10%)
Sex		
Female	109/335 (33%)	18/324 (6%)
Male	135/425 (32%)	34/426 (8%)
Race		
Caucasian	152/476 (32%)	23/463 (5%)
Non-Caucasian	92/284 (32%)	29/287 (10%)
Region		
Asia / Pacific	90/216 (42%)	26/211 (12%)
Europe	75/203 (37%)	12/203 (6%)
North America	79/341 (23%)	14/336 (4%)
Total	244/760 32%	52/750 7%

Source: Reviewer

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

There were no statistical issues identified during the review. The studies were conducted as planned, and any protocol amendments did not impact the analysis or interpretation of the results. Dropouts were higher in the placebo group, and subjects who discontinued were coded as smokers (non-responders) from that point on. Missing data on the main efficacy measures did not impact the coding of responders or the results.

The applicant proposed that the results of Study 1075 be added to Section 14 of the label along with a change in the Dosing and Administration section to describe the reduce-to-quit strategy. The study description matches the style of the previous studies in the existing label, and is appropriate.

5.2 Labeling Review

The goal of this supplement application is to add an indication for a gradual approach to quitting smoking. The following wording is proposed for the Dosage and Administration section of the label:

(b) (4)

Study 1075 is described in Section 14.5, with appropriate details regarding the design and representation of the results. In the applicant's proposed labelling, (b) (4) The timeframes for the efficacy endpoints in this study (weeks 15-24; Weeks 21-52) are not the same as the timeframes reported for other efficacy studies due to the alternative timeframe for quitting with the reduce to quit approach.

The following is the current proposed language for Study 1075:

> 14.5 Gradual Approach to Quitting Smoking
> CHANTIX was evaluated in a 52-week double-blind placebo-controlled study of 1,510 subjects who were not able or willing to quit smoking within four weeks, but were willing to gradually reduce their smoking over a 12 week period before quitting. Subjects were randomized to either CHANTIX 1 mg twice daily (n=760) or placebo (n=750) for 24 weeks and followed up post-treatment through week 52. Subjects were instructed to reduce the number of cigarettes smoked by at least 50 percent by the end of the first four weeks of treatment, followed by a further 50 percent reduction from week four to week eight of treatment, with the goal of reaching complete abstinence by 12 weeks. After the initial 12-week reduction phase, subjects continued treatment for another 12 weeks. Subjects treated with CHANTIX had a significantly higher Continuous Abstinence Rate compared with placebo at weeks 15 through 24 (32% vs 7%) and weeks 21 through 52 ((b) (4) vs (b) (4)).

The above description and results from Study 1075 are consistent with my review.

5.3 Conclusions and Recommendations

The goal of this single study was to show superiority of varenicline over placebo for the aid of smoking cessation in smokers who were not willing or able to make an abrupt quit attempt, but who were willing to follow a reduce-to-quit schedule with the goal of complete abstinence by Week 12. Based on my review of this study, I conclude there is sufficient evidence of efficacy to support adding these results to the Clinical Studies section of the currently approved label for varenicline.

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

/s/

KATHERINE B MEAKER
06/08/2016

DAVID M PETULLO
06/08/2016
I concur.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021928/S-039

OTHER REVIEW(S)

Division of Anesthesia, Analgesia, and Addiction Products

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: NDA 21928/ S-039 & S-041
Name of Drug: Chantix (varenicline) Tablets; 0.5 mg and 1 mg
Applicant: Pfizer, Inc.

Labeling Reviewed

Submission and Receipt Date: S-039: October 13, 2015
S-041: July 21, 2016

Background and Summary Description:

Supplement S-039 proposes changes to the **DOSAGE AND ADMINISTRATION**, and **CLINICAL STUDIES** sections of the Package Insert, and to the approved risk evaluation and mitigation strategy (REMS) for Chantix, including revisions to the Medication Guide to support the reduce-to-quit dosing paradigm.

Supplemental S-041 proposes revisions to the **WARNINGS AND PRERCAUTIONS**, **ADVERSE REACTIONS, PATIENT COUNSELING INFORMATION** sections, and (b) (4) regarding the risk of somnambulism.

Review

The revised labeling submitted under S-039, and S-041on August 2, 2016, was compared to labeling approved on October 15, 2014, for S-037.

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	August 3, 2016
Regulatory Project Manager	Date
Parinda Jani	August 3, 2016
Chief, Project Management Staff	Date

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

---

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
08/04/2016

PARINDA JANI
08/05/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Pregnancy and Lactation Labeling Rule (PLLR) Labeling Review

Date: 06-08-2016

From: Leyla Sahin, M.D.
Medical Officer, Maternal Health Team
Division of Pediatric and Maternal Health

Through: Tamara Johnson, M.D., M.S.
Team Leader, Maternal Health Team
Division of Pediatric and Maternal Health

Lynne P. Yao, M.D.
Director,
Division of Pediatric and Maternal Health

To: Division of Anesthesia, Analgesia, and Addiction Products

Drugs: Chantix (varenicline) tablets ; NDA 21928/S039

Subject: Pregnancy and Lactation Labeling Rule (PLLR) Labeling as part of Labeling Supplement

Applicant: Pfizer

Materials Reviewed:
- Applicant's proposed labeling
- Approved labeling (11-2014)
- Literature review

Consult Question: Please advise regarding Pregnancy and Lactation Labeling Rule (PLLR) Labeling

INTRODUCTION

The applicant submitted a labeling supplement for Chantix (varenicline) tablets on October 13, 2015 that includes the addition of data from a post-marketing study and includes labeling in the format of the Pregnancy and Lactation Labeling Rule (PLLR). The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) consulted the Division of Pediatric and Maternal Health (DPMH) on November 20, 2015, to assist with reviewing the Pregnancy and Lactation subsections of labeling.

BACKGROUND

Product Background

Chantix (varenicline) was approved as an aid to smoking cessation in 2006. It is a partial agonist at α4β2 nicotinic acetylcholine receptors that prevents nicotine receptor binding and nicotine-mediated stimulation of the mesolimbic dopamine system, which is thought to underlie the reward and behavioral reinforcement associated with smoking dependence. Other FDA approved smoking cessation drug products include bupropion and nicotine replacement therapies.

Approved varenicline labeling includes language that states that Chantix should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Nonclinical reproductive and developmental toxicity studies in pregnant rabbits at exposures 50 times the human exposure (based on AUC) at the maximum recommended human dose (MRHD) of varenicline resulted in reduced fetal weights. In addition, treatment of pregnant rats with exposures 36 times the human exposure at the MRHD resulted in increased auditory startle response in offspring.

Smoking in Pregnancy

According to the American College of Obstetricians and Gynecologists, smoking is one of the most important modifiable causes of poor pregnancy outcomes in the Unites States, and is associated with maternal, fetal, and infant morbidity and mortality.[1]

The Surgeon General regularly reviews the medical literature on the effects of smoking and updates its report based on the most current data. The 2014 Surgeon General's Report on the Health Consequences of Smoking states that there is sufficient evidence that show that smoking during pregnancy causes increased risks of orofacial clefts, premature rupture of membranes, placenta previa, placental abruption, ectopic pregnancy, fetal growth restriction and low birth weight, stillbirth, preterm delivery and shortened gestation, neonatal death, sudden infant death syndrome and reduction of lung function in infants.[2] The Surgeon General's report includes a review of published studies on the association between smoking during pregnancy and orofacial clefts. A meta-analysis of 38 studies published between 1959 and 2010 showed an increased risk for orofacial clefts in the infants of women who smoked during pregnancy, with a pooled OR of 1.28 (95% CI 1.2-1.36).[3] Restriction of the analysis to include only studies that adjusted for

[1] American Colleges of Obstetricians and Gynecologists Committee Opinion Number 471. Smoking Cessation During Pregnancy. November 2010

[2] http://www.surgeongeneral.gov/library/reports/50-years-of-progress/

potential confounders did not change the results (adj OR 1.26; 95% CI 1.18-1.34). An earlier meta-analysis of 24 studies published between 1974 and 2001 showed an association between maternal smoking and orofacial clefts (RR 1.34;95% CI 1.25-1.44).[4] Studies that published after the 2010 cutoff date of the recent meta-analysis also confirmed the association between maternal smoking and orofacial clefts.[5]

Review of published data

Pregnancy

A prescription database study that identified dispensing of varenicline in females of reproductive potential reported on 23 varenicline-exposed pregnant women who elected to complete a questionnaire on pregnancy outcomes.[6] Among 16 pregnancies that resulted in 17 live births (1 set of twins), there were no infants with major malformations.

There is a case report of a woman who used varenicline prior to conception and through the entire pregnancy and delivered a full term healthy infant.[7]

Lactation data

There are no published data on varenicline levels in milk, the effects on the breastfed infant, or the effects on milk production.

Review of unpublished data

DPMH reviewed data from a post-marketing requirement (PMR) study in a review in DARRTS dated 5-6-2016. These interim data on 317 first trimester varenicline exposures were based on Swedish and Danish birth register data, and it is anticipated that the final report will be submitted 9-2016. These data showed that the prevalence of major malformations and adverse perinatal outcomes was similar in the varenicline cohort, the exposed cohort and the reference cohort (pregnant women who smoked but did not take varenicline and pregnant women who did not smoke or take varenicline). The occurrence of 3 ventricular septal defects (VSDs) out of 12 major malformations in the varenicline exposed cohort suggest that a potential safety signal may be emerging, however there are no data on the prevalence of VSDs in the unexposed and the reference cohort to allow a comparison, therefore it is not possible to draw any conclusions.

Nonclinical Data

---

[3] Hackshaw A, Rodeck C, Boniface S. et al. Maternal smoking in pregnancy and birth defects: a systematic review based on 173 687 malformed cases and 11.7 million controls. Human Reproduction Update. 2011 Vol 17, No.5, 589-604.

[4] Little J, Cardy A, Munger R. Tobacco smoking and oral clefts: a meta-analysis. Bulletin of the World Health Organization. 2004, 82 (3).

[5] Supplemental data Hackshaw A, Rodeck C, Boniface S. et al.

[6] Harrison-Woolrych M, Paterson H, Tan M. Exposure to the smoking cessation medicine varenicline during pregnancy: a prospective nationwide cohort study. Pharmacoepidemiol Drug Saf. 2013; 22(10):1086-1092.

[7] Kaplan YC, Olgac Dundar N, Kasap B, et al. Pregnancy Outcome after varenicline exposure in the first trimester. Case Reports in Obstetrics and Gynecology. 2014; 263981.

No new nonclinical data were submitted with this supplement. Nonclinical sections for Pregnancy and Lactation were revised to conform to PLLR by Dr. Carlic Huynh and Dr. Dan Mellon.

Pregnancy and Lactation Labeling Rule (PLLR)

The Pregnancy and Lactation Labeling Rule (PLLR) went into effect on June 30, 2015.[8] The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation. Additionally, information on pregnancy testing, contraception, and infertility that has been located in other sections of labeling are now presented in a new subsection, 8.3 Females and Males of Reproductive Potential, under Use in Specific Populations (8). Specifically, the pregnancy categories (A, B, C, D and X) will be removed from all prescription drug and biological product labeling and a new format will be required for all products that are subject to the 2006 Physicians Labeling Rule, to include information about the risks and benefits of using these products during pregnancy and lactation.

DISCUSSION

Pregnancy

Available pregnancy data are limited to a published review of 23 pregnancies, one case report, and interim PMR data from the Swedish and Danish birth registers, and it is not possible to draw any conclusions on the safety of varenicline in pregnancy. However, the occurrence of 3 ventricular septal defects (VSDs) out of 12 major malformations in the varenicline exposed cohort suggest that a potential safety signal may be emerging and will need to be monitored with follow up information. At the present time, DPMH recommends not adding any human data to labeling. The PMR data will be re-assessed following submission of the final study report, which is anticipated to be submitted in September 2016. Consideration of addition of these data to labeling can be assessed at that time.

The perinatal risks associated with smoking are well characterized, therefore it is appropriate to add this information to Clinical Considerations, under the Disease-associated maternal and/or embryo/fetal risk subheading. In a labeling meeting on 6-8-2016, DAAAP was concerned that the addition of this information may be misconstrued as implying that use of Chantix during pregnancy decreases these events. Because there are no data that support that use of Chantix decreases these events during pregnancy, there was consensus that the following statement should be added: “It is not known whether quitting smoking with Chantix during pregnancy reduces these risks”.

The Surgeon General has concluded that there is sufficient evidence that shows that smoking during pregnancy causes an increased risk of orofacial clefts, compared to pregnant women who do not smoke. Although the magnitude of the effect is relatively modest (approximately 30% increase in risk), the Surgeon General Report comments that it is possible that there may be misclassification due to under-reporting of maternal smoking, and that the risk estimate may in

[8] Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling (79 FR 72063, December 4, 2014).

fact be higher. Orofacial clefts are among the most common major birth defects in the United States, with approximately 1 in 870 live births affected by cleft lip with or without cleft palate, and 1 in 1500 births affected by cleft palate alone.[9] Therefore, smoking cessation during pregnancy has the potential to have a significant public health impact. The addition of the increase in risk of orofacial clefts to the Risk Summary is appropriate under PLLR.

Lactation

There are no data to inform the safety of varenicline in the breastfed infant. Under PLLR, it is appropriate to describe the lack of clinical data to inform risk, and include the following risk/benefit statement in subsection 8.2 Lactation, under the Risk Summary heading:

"The lack of clinical data during lactation precludes a clear determination of the risk of CHANTIX to an infant during lactation; however the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for CHANTIX and any potential adverse effects on the breastfed child from CHANTIX or from the underlying maternal condition".

In addition, it is reasonable to add advice to monitor breastfed infants for seizures and vomiting, which are labeled adverse reactions in adults.

CONCLUSION

The Pregnancy and Lactation subsections of labeling were structured to be consistent with the PLLR. DPMH has the following recommendations for Chantix labeling:

- 8.1 Pregnancy
  - The "Pregnancy" subsection of Chantix labeling was formatted in the PLLR format to include "Risk Summary", "Clinical Considerations", and "Data" sections.
- 8.2 Lactation
  - The "Lactation" subsection of Chantix labeling was formatted in the PLLR format to include the "Risk Summary" and "Data" sections.

DPMH LABELING RECOMMENDATIONS

DPMH discussed our labeling recommendations with DAAAP. DPMH recommendations are below and reflect the discussions with DAAAP. **See final labeling for all of the labeling revisions negotiated with the applicant.**

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available human data on the use of CHANTIX in pregnant women are not sufficient to inform a drug associated risk. Smoking during pregnancy is associated with maternal, fetal, and neonatal

[9] Honein, M, Rasmussen S, Reefhuis J, et al. Maternal smoking and environmental tobacco smoke exposure and the risk of orofacial clefts. Epidemiology 2007;18:226-233.

risks *[see Clinical Considerations]*. In animal studies, varenicline did not result in major malformations but caused decreased fetal weights in rabbits when dosed during organogenesis at exposures equivalent to 50 times the exposure at the maximum recommended human dose (MRHD). Additionally, administration of varenicline to pregnant rats during organogenesis through lactation produced developmental toxicity in offspring at maternal exposures equivalent to 36 times human exposure at the MRHD *[see Data]*.

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

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

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

Data

Animal Data

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

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

8.2 Lactation

Risk Summary

There are no data on the presence of varenicline in human milk, the effects on the breastfed infant, or the effects on milk production. In animal studies varenicline was present in milk of lactating rats *[see Data]*. However, due to species-specific differences in lactation physiology, animal data may not reliably predict drug levels in human milk. The lack of clinical data during lactation precludes a clear determination of the risk of CHANTIX to an infant during lactation; however the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for CHANTIX and any potential adverse effects on the breastfed child from CHANTIX or from the underlying maternal condition.

Clinical Considerations
Monitor breastfed infants for seizures and vomiting.

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

17 PATIENT COUNSELING INFORMATION

Pregnancy and Lactation

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

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

/s/

LEYLA SAHIN
06/08/2016

TAMARA N JOHNSON
06/08/2016

LYNNE P YAO
06/09/2016

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

PATIENT LABELING REVIEW

Date:	May 26, 2016
To:	Sharon Hertz, MD Director **Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** L. Shenee' Toombs, Pharm.D. Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	CHANTIX (varenicline)
Dosage Form and Route:	Tablets
Application Type/Number:	NDA 021928
Supplement Number:	S-039
Applicant:	Pfizer, Inc.

1 INTRODUCTION

On October 13, 2015, Pfizer, Inc. submitted for the Agency's review a Prior Approval Supplement (PAS)- Efficacy to their approved New Drug Application (NDA) 021928/S-039 for CHANTIX (varenicline) tablets. In this PAS, the Applicant proposes changes to the Prescribing Information (PI) based on clinical trial data from the study titled, "A Phase 4, Multi-National, Randomized, Double-Blind, Placebo-Controlled Study to E valuate the Efficacy and Safety of Varenicline Compared to Placebo for Smoking Cessation Through Reduction". The Applicant also proposes modifications to the approved Risk Evaluation and Mitigation Strategy (REMS) for Chantix (varenicline) tablets, including revisions to the Medication Guide (MG). CHANTIX (varenicline) tablets was originally approved on May 10, 2006, and is indicated for use as an aid to smoking cessation treatment.

Additionally, based on a review of FAERS reports and the medical literature for somnambulism associated with CHANTIX (varenicline) by the Division of Pharmacovigilance II (DPV II) dated December 18, 2015, as requested by the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP), the PI has been updated with a new Warning and Precaution for somnambulism.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by DAAAP on November 20, 2015, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for CHANTIX (varenicline) tablets.

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

2 MATERIAL REVIEWED

- Draft CHANTIX (varenicline) tablets MG received on October 13, 2015, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP May 16, 2016.
- Draft CHANTIX (varenicline) tablets Prescribing Information (PI) received on October 13, 2015, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 16, 2016.
- Approved CHANTIX (varenicline) tablets labeling dated October 15, 2014
- Division of Pharmacovigilance II (DPV II) Review dated December 18, 2015

3 REVIEW METHODS

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

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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

---

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

/s/

SHARON R MILLS
05/26/2016

LATOYA S TOOMBS
05/27/2016

BARBARA A FULLER
05/27/2016

LASHAWN M GRIFFITHS
05/27/2016

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

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

Memorandum

Date: May 27, 2016

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

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

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

Subject: NDA 021928/S-039
OPDP labeling comments for CHANTIX® (varenicline) tablets
Labeling Review

OPDP has reviewed the proposed package insert (PI) for CHANTIX® (varenicline) tablets (Chantix) that was submitted for consult on November 20, 2015. Comments on the proposed PI are based on the version sent via email from Ayanna Augustus (RPM) on May 16, 2016 entitled "Chantix label 05 16 16.doc ".

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

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

Thank you for the opportunity to comment.

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

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

---

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

/s/

LATOYA S TOOMBS
05/27/2016

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	March 18, 2016
Requesting Office or Division:	Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Application Type and Number:	NDA 21928/S-039
Product Name and Strength:	Chantix (varenicline tartrate) tablet, 0.5 mg and 1 mg
Product Type:	Single-ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Pfizer, Inc.
Submission Date:	October 13, 2015
OSE RCM #:	2015-2500
DMEPA Primary Reviewer:	Millie Shah, PharmD, BCPS
DMEPA Team Leader:	Vicky Borders-Hemphill, PharmD

1 REASON FOR REVIEW

Pfizer, Inc. submitted a prior approval efficacy supplement (S-039) for labeling revisions based on the study, "*A Phase 4, Multi-National, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Varenicline Compared to Placebo for Smoking Cessation Through Reduction*." Thus, the Division of Analgesia, Anesthesia, and Addiction Products (DAAAP) requested that we review the labeling revisions from a medication error perspective.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C-N/A
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E
Other	F-N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Pfizer, Inc. submitted supplement 039, which includes labeling revisions to introduce information for people who are not willing or able to make an abrupt quit attempt, but who are willing to reduce their smoking with the ultimate goal of quitting.

We performed a risk assessment of the proposed revisions to the prescribing information (PI) and medication guide (MG) to identify deficiencies that may lead to medication errors and other areas for improvement.

Prescribing Information

Our review of the PI identified error-prone symbols in the *Dosage and Administration* section of the Highlights of Prescribing Information and Full Prescribing Information. Thus, we provide a recommendation in Section 4.1 below to remove error-prone symbols.

Medication Guide

Our review of the MG did not identify vulnerabilities to medication errors. Thus, we do not have recommendations at this time.

FAERS and ISMP Newsletter Search

We performed a FAERS and ISMP Newsletter search to inform our review. Our FAERS search identified several wrong strength errors between the 0.5 mg and 1 mg strengths. Our review of the container label and carton labeling determined that the strength is clearly and prominently displayed and the 0.5 mg and 1 mg strengths are adequately differentiated. Thus, we do not have recommendations to mitigate the risk for these errors. Additionally, we identified cases that describe patients restarting therapy with the 1 mg strength instead of the 0.5 mg strength. The cases do not provide enough information to determine a root cause or an outcome. Our review of the prescribing information did not identify areas for improvement to mitigate the risk for these errors. Thus, we do not have recommendations at this time.

4 CONCLUSION & RECOMMENDATIONS

We identified areas in the Prescribing Information that can be improved for clarity to promote safe use of this product.

If you have further questions or need clarifications, please contact Davis Mathew, OSE Project Manager, at 240-402-4559.

4.1 RECOMMENDATIONS FOR THE DIVISION

We have revised the Prescribing Information (See Appendix G) and have provided a detailed summary below for review and consideration by DAAAP.

A. Full Prescribing Information
   1. We recommend [redacted] (b) (4) "less than" in the *Dosage and Administration* section to prevent misinterpretation and confusion.[1]

B. Highlights of Prescribing Information
   1. See A.1.

[1] Food and Drug Administration. *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*, April 2013. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Chantix that Pfizer, Inc. submitted on October 13, 2015.

Table 2. Relevant Product Information for Chantix	
Initial Approval Date	May 10, 2006
Active Ingredient	varenicline tartrate
Indication	for use as an aid for smoking cessation treatment
Route of Administration	oral
Dosage Form	tablet
Strength	0.5 mg and 1 mg
Dose and Frequency	• Starting week: 0.5 mg once daily on days 1-3 and 0.5 mg twice daily on days 4-7 • Continuing weeks: 1 mg twice daily for a total of 12 weeks • An additional 12 weeks of treatment is recommended for successful quitters to increase likelihood of long-term abstinence
How Supplied	• Starting 2 week card: 0.5 mg x 11 tablets and 1 mg x 14 tablets • Continuing 2 week card: 1 mg x 28 tablets • Starting 4-week card: 0.5 mg x 11 tablets and 1 mg x 42 tablets • Continuing 4-week card: 1 mg x 56 tablets • Starting Month Box: 0.5 mg x 11 tablets and 1 mg x 42 tablets • Continuing Month Box: 1 mg x 56 tablets • 0.5 mg - bottle of 56 • 1 mg - bottle of 56
Storage	Store at 25ºC (77ºF); excursions permitted to 15–30ºC (59–86ºF) (see USP Controlled Room Temperature).
Container Closure	blister cards and bottles

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On January 27, 2016, we searched the L:drive and AIMS using the term, Chantix, to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified three previous label/labeling reviews.

Table 3. Previous DMEPA Reviews		
RCM#	**Date**	**Summary**
2010-1359 and 2007-2020[2]	November 23, 2010	We provided recommendations for the container label and carton labeling (S-018), for the two-week professional sample pack and recommended to (b) (4) We also provided additional labeling recommendations to clarify the instruction for use.
2011-1032[3]	June 7, 2011	We evaluated the implementation of our recommendations made in OSE review #2010-1359 and label and labeling samples submitted via email dated May 19, 2011 and found them acceptable.
2014-780[4]	July 28, 2014	We evaluated the medication error potential of replacing the 2-week trade packaging configurations with 4-week trade packaging configurations. We determined that the new packaging configuration does not create new risk for medication errors and provided recommendations to improve the labels and labeling. We determined our recommendations were accepted.

[2] Najam L. Label and Labeling Review for Chantix (varenicline) tablets (NDA 021928/S-018). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2010 NOV 23. 13 p. OSE RCM No.: 2010-1359 and 2007-2020.

[3] Merchant L. Label and Labeling Review for Chantix (varenicline) tablets (NDA 021928/S-024). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2011 JUN 07. 6 p. OSE RCM No.: 2011-1032.

[4] Borders-Hemphill V. Label and Labeling Review for Chantix (varenicline) tablets (NDA 021928/S-037). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 JUL 28. 63 p. OSE RCM No.: 2014-780.

APPENDIX C. HUMAN FACTORS STUDY-N/A

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On January 27, 2016, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

Table 4. ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care, Community/Ambulatory Care, and Nursing
Search Strategy and Terms	Match Exact Word or Phrase: Chantix

D.2 Results

Our search retrieved 28 newsletters, but after further evaluation, we did not identify any medication error cases that were relevant to this review and could be addressed by label and labeling revisions.

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

E.1 Methods

DMEPA previously performed a search of the FDA Adverse Event Reporting System (FAERS), reported in OSE Review #2014-780[5] (dated July 28, 2014) to identify medication errors related to use of Chantix. Therefore, we searched FAERS on January 21, 2016 and limited our search to cases with an event date since our previous search from June 12, 2014 to January 1, 2016. We used the criteria in Table 5, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the labels and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when the reporter provided sufficient information.[6]

Table 5: FAERS Search Strategy	
Date Range	**June 12, 2014 to January 1, 2016**
Product	**Chantix** [product name]
Event (MedDRA Terms)	**DMEPA Official FBIS Search Terms Event List:**

[5] Borders-Hemphill V. Label and Labeling Review for Chantix (varenicline) tablets (NDA 021928/S-037). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 JUL 28. 63 p. OSE RCM No.: 2014-780.

[6] The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website http://www.nccmerp.org/pdf/taxo2001-07-31.pdf.

	Contraindicated Drug Administered (PT) Drug Administered to Patient of Inappropriate Age (PT) Inadequate Aseptic Technique in Use of Product (PT) Medication Errors (HLGT) Overdose (PT) Prescribed Overdose (PT) Prescribed Underdose (PT) Product Adhesion Issue (PT) Product Compounding Quality Issue (PT) Product Formulation Issue (PT) Product Label Issues (HLT) Product Packaging Issues (HLT) Product Use Issue (PT) Underdose (PT)
Country (derived)	**USA**

E.2 Results

Our search identified 71 cases, of which 22 described errors relevant for this review. We identified 13 wrong strength errors where the patient received the 1 mg strength instead of the 0.5 mg strength or vice versa. Our review of the container label and carton labeling determined that the strength is clearly and prominently displayed and the 0.5 mg and 1 mg strengths are adequately differentiated. Thus, we do not have recommendations to mitigate the risk for these errors.

We identified 9 cases that describe patients restarting therapy with the 1 mg strength instead of the 0.5 mg strength. The cases do not provide enough information to determine a root cause or an outcome. Our review of the prescribing information did not identify areas for improvement to mitigate the risk for these errors. Thus, we do not have recommendations at this time.

We excluded 49 cases because they did not identify medication error cases that were relevant to this review and could be addressed by label and labeling revisions.

E.3 List of FAERS Case Numbers

Table 6: FAERS Case Numbers and Narratives	
FAERS Case Number	**Narrative**
10267540	This is a spontaneous report from a non-clinical-study program, Chantix CV Label Update Teleservices Scripts by a contactable consumer. A 48 year old White female consumer started to receive varenicline tartrate (CHANTIX) (Expiration date: 07Mar2015) at an unknown dose which she stopped on an unknown date and restarted on an unknown date in Nov2013 at an unknown dose and frequency which she stopped on an unknown date and again restarted taking it since an unknown date in 2014 at 0.5mg at an unknown frequency to quit smoking. One package of varenicline had an expiration date of 07Mar2015. Relevant medical history included ongoing endometriosis and ongoing pain both since an unknown date. Relevant concomitant medication included hydrocodone bitartrate and acetaminophen (VICODIN) since an unknown date at an unknown dose and frequency for pain. The consumer reported that she had tried varenicline numerous times and quit each time after 5th day but after the first time she only used the 1mg tablets and this last time she was given 0.5 mg and they did not work. The consumer reported that since an unknown date in Jun2014 she did not receive varenicline tartrate as prescribed (elaborated that instead of getting continuation full strength pack she received starter pack from her pharmacy) which did not work for her (at a dose of 0.5mg at an unknown frequency). The action taken in response to the event for varenicline tartrate was unknown. The outcome of the event was unknown. Follow up (25Jun2014): New information from a contactable consumer via a non-clinical-study program, CHANTIX CV Label Update Teleservices Scripts, included: patient demographics, suspect drug details, medical history, concomitant medications and new event (instead of getting continuation full strength pack she received starter pack)
10447065	This is a spontaneous report from non-clinical study program Chantix CV Label Update Teleservices Scripts. A non contactable female consumer of an unspecified age and ethnicitreported that she started to receive varenicline tartrate (CHANTIX), at 1 mg unspecified frequency and 0.5 mg unspecified frequency, via an unspecified route of administration from an unspecified date to stop smoking. The consumer's medical history was not reported. The consumer's concomitant medications were not reported. The consumer reported that she couldn't take the 1 mg of varenicline because of the nausea. The consumer took just the 0.5 mg or whatever it was. The consumer also reported that her doctor had written on there the 0.5 mg, so they shouldn't have even really been giving her the kit, because the consumer believed the kit included the 5 mg and the 1 mg. And the consumer wondered if it's going to be cheaper in the long run because she thought she could cut those 1 mg in half like she was doing before so she wasn't getting the nausea. The consumer didn't mind the dreams. The consumer reported that as soon she started the 0.5 mg, she was dreaming. The action taken and events outcome were unknown. No follow up attempts possible. No further information expected.
10484326	This is a spontaneous report from a non-clinical-study program Pfizer RXPathways and Chantix CV Label update Teleservices Scripts. A contactable female consumer of an unspecified age and ethnicity started to receive venlafaxine hydrochloride (EFFEXOR XR), at 225 mg one daily from Dec2013 for depression. The consumer medical history included a car accident in 2003, when her seizure disorder started (she was treated with gabapentin, she went to the hospital many times). She is fine

	now. The consumer's concomitant medications included: citalopram hydrobromide (CELEXA) since 2014, butalbital, caffeine, paracetamol (FIORECET) since 2009, gabapentin (NEURONTIN) since 2003 for seizure disorder, (KLONOPIN) since 2014 for seizure disorder, all ongoing. The action taken in response to the event for venlafaxine hydrochloride was unknown. The outcome of the event was unknown. Consumer clarified that she had never taken varenicline tartrate (CHANTIX), she was given a prescription and that medication was from Pfizer RXPathways program. She mentioned that she received the continuation pack about a month ago and not the starter pack from the Pfizer RXPathways program so she had not taken it. She has not received the starter pack yet. The action taken for varenicline tartrate was not applicable. Follow up (28Oct2014): New information reported from a non Clinical Study Program Chantix CV Label update Teleservices Scripts by a contactable consumer includes: suspect drug data (had not taken Chantix) and event data (added: Drug dispensing error). Follow-up (01Dec2014): New information from a contactable consumer includes: drug data (onset date, dose, frequency, indication), deleted seizure disorder as a serious adverse event and added to medical history, prior to venlafaxine, medical history (seizure disorder, car accident), and concomitant medications case downgraded to non-serious.
10485038	This is a spontaneous report from a contactable consumer via the non-clinical-study program Pfizer RXPathways. A 58-year-old White male patient started to receive sildenafil citrate (VIAGRA), dates, dose, route, frequency and indication were unspecified; varenicline tartrate (CHANTIX), lot number was D10493730 and the expiration date was Jan2017, dates, dose, route to quit smoking, and nitroglycerin (NITROSTAT), dates, dose, route, frequency and indication were unspecified. The patient's medical history included ongoing high blood pressure since an unknown date and the patient's concomitant medications included lisinopril since an unknown date at a dose of 20 mg daily for high blood pressure. On an unspecified date, the patient experienced a heart attack with an outcome of unknown. The action taken in response to the event for sildenafil citrate was unknown, for varenicline tartrate was unknown and for nitroglycerin was unknown. Subsequently the same contactable consumer reported he has had no bad reactions with CHANTIX, VIAGRA and NITROSTAT. Upon receipt of follow up, the patient reported that on an unknown date he was dispensed with 6 packs of blue pills of varenicline tartrate and there were no white pills elaborated as white pills were also supposed to be provided to him. Relevant laboratory data was none. The patient was not on varenicline tartrate therapy at the time of report. The outcome of the event, dispensed with 6 packs of blue pills of the medication and there were no white pills, was unknown. Follow-up (03Oct2014): New information from the same contactable consumer included denial of any bad reactions with CHANTIX, VIAGRA and NITROSTAT. Follow-up (10Oct2014): The initial case was missing the following minimum criteria: adverse event. Upon receipt of follow up information on 10Oct2014, this case now contains all required information to be considered valid. New information received from a contactable consumer via a non clinical study program, Pfizer RXPathways, included patient age, ethnicity, gender, lot number, expiration date of CHANTIX, indication of CHANTIX, medical history, concomitant medication, a new event "dispensed with 6 packs of blue pills of the medication and there were no white pills", and no lab data.
10513541	This is a spontaneous report from non-clinical-study program (Chantix CV Label Update Teleservices Scripts). A non-contactable 63-year-old Caucasian female consumer started to receive oral varenicline tartrate (CHANTIX) from Sep2014 for approximately 1 month at 0.5 mg once daily to stop smoking, filling the prescription on 26Aug2014, but did not start the medicine until early Sep2014. The medical history and concomitant medications were not reported. The consumer stated she

	was very committed to quit smoking, and had also stopped drinking coffee. She stated the headaches began right away after starting the medicine, but were gone after the first week, about the middle of Sep2014. She also had issues with not being able to go to sleep, starting after about the first week, about the middle of Sep2014, but it went away. She was now having sleep issues again after being off varenicline tartrate. The nausea started with the increase in dose from 0.5 mg to the 1 mg dose in Sep2014. She experienced vomiting after about 2-3 days, which would be in early Sep2014. With an increase in the amount she ate for breakfast the vomiting stopped immediately, with just a tiny bit of nausea she could deal with. After the first month the nausea was very slight, which she combats with a full glass of water and a full meal with a dose. The consumer stated her agitation had intensified since stopping varenicline tartrate. The consumer went to get her second month supply in Sep2014, but the physician had written the prescription wrong, and wrote for another 4 starter kits, and she was unable to fill as only 1 starter kit was allowed. The consumer had called her physician for another prescription, but it could take 72 hours or longer to refill. The consumer stated she was experiencing withdrawal in Oct2014. The action taken for varenicline tartrate was permanently withdrawn in Oct2014. The outcome for the events sleep issues / not being able to go to sleep, increased agitation, withdrawal symptom was not recovered, for nausea was recovering, for vomiting and headache was recovered in Sep2014. The outcome of other event was unknown. No follow up attempts possible. No further information expected.
10530291	This is a spontaneous report from a non-clinical-study program (Chantix CV Label Update Teleservices Scripts) from a contactable consumer. A female patient of unspecified age and ethnicity reported taking varenicline tartrate (CHANTIX) for an unspecified indication. Medical history and concomitant medications were not provided. Past drug history included varenicline tartrate use a few years ago, which 'worked fine' but she stopped as she could not afford it. The patient reported that the doctor gave her 6 months samples of varenicline tartrate, but they were all blue (1 mg, expires in 2017); she did not receive the starter pack. The patient reported that her doctor gave her varenicline tartrate that expired in Apr2014 and she took that for 7 days (a couple weeks ago), but it did not work. The patient reported that the only side effect she experienced while on varenicline tartrate was vivid dreams. The action taken with varenicline tartrate and outcome of the events were not provided.
10540287	This is a spontaneous report from a Non Clinical Study Program, Chantix CV Label Update Teleservices Scripts for a contactable consumer. This 39-year-old Caucasian male consumer started to receive varenicline tartrate (CHANTIX), (NDC: 0069047102), from an unspecified date in 2014 at starter pack for unknown indication. Medical history included ongoing multiple sclerosis since he was 21 years old. Concomitant medication included fentanyl transdermal system for pain at 100mcg/HR and he took it every 48 hours, tizanidine 2mg tablet at 3 tablets two times a day (3 tablets in the morning and 3 tablets in the evening), zolpidem (the generic for Ambien) at 12.5mg just one, hyoscyamine 10540287at 0.357mg once tablet at night and natalizumab (TYSABRI) infusion once a month and did not know the milligrams he was taking. The consumer reported he quit smoking 26 days ago (Sep2014) on varenicline and was feeling sick to his stomach in 2014. His healthcare professional (HCP) wanted him to take varenicline for 4 months and the consumer got his second prescription of varenicline but was given and dispensed with starter pack again when it should have been the continuing pack. The consumer mentioned that he was still feeling pukey and sick to his stomach. His HCP wanted him to take varenicline for 4 months and he kept getting the starter pack instead of the continuing pack. He mentioned he was still taking varenicline and was on his continuous pack. The consumer mentioned that he started feeling sick to his stomach and pukey in his

	first week of taking continuous pack. The action taken in response to the events for varenicline tartrate was dose not changed. The outcome of the event, sick to his stomack/feeling pukey, was not recovered. The outcome of the other event was unknown.
10777420	This is a spontaneous report from a non-clinical-study CHANTIX CV Label Update Teleservic via a contactable patient (patient). A 66-year-old African-American female patient started to receive varenicline tartrate (CHANTIX) (Lot #: E10060030-Expires: Nov2016) from 15Jan2015 to stop smoking. Past medical history and concomitant medications were not reported. The patient received two starter boxes and two continuing boxes of varenicline tartrate on an unspecified date. She wanted to know if she should use the second starter box. She stated that the pharmacy had dispensed 2 starter boxes and 2 continuing boxes instead of 1 starter box and 3 continuing boxes. Patient stated she originally reported that she did not receive enough medication. After opening the packaging the patient realized she had more medication than she should have. Patient stated that was a medication error due to the dispensing of the medication. Patient stated she was given two starter packs and two continuing packs. Patient stated she will not be returning any of the medication because she is going to continue to take the medication. Patient reported she only takes 1mg of CHANTIX per day. Patient is currently taking two 0.5mg tablets. CHANTIX 1 mg twice a day made her sick. Patient also reports that she has not taken any CHANTIX yet on 06Feb2015. CHANTIX box with all packs of both 1mg and 0.5mg tablets: Lot number: E10060030. Expiration date: Nov 2016. NDC number: 0069-0471-02. Starter pack taking now: CHANTIX 0.5mg tablets: Lot number: D10414932. Expiration date: Nov 2016. NDC number: 0069-0471-01. Continuing pack: CHANTIX 1mg tablets: Lot number: E10060030. Expiration date: Nov 2016. NDC number: 0069-0469-11. The action taken for varenicline was dose not changed. The outcome of the events was unknown. Follow-up (03Feb2015): New information received from a non-clinical-study program CHANTIX CV Label Update Teleservices Scripts via a contactable patient (patient) includes: patient demographic, drug data, reaction data (added nauseated) and action taken. Follow-up (06Feb2015): This is a spontaneous follow-up report from a contactable patient includes: reaction data (added event "1 mg twice a day made her sick") and drug data (LOT NO. and Expiration date).
10782052	This is a spontaneous report from a non-clinical-study program Chantix CV label update Teleservices script from a contactable consumer. A 58-year-old Caucasian female patient started to receive varenicline tartrate (CHANTIX) (Lot # E10288530, Expiration Date Sep2016, NDC: 0069046912) orally from 29Jan2015 at 1mg daily to quit smoking. She also reported started to receive varenicline (Lot: D10288530, Expiration: 21Jan2016, NDC: 0069-0469-11) at 1mg, frequency unknown on 29Jan2015. Medical history ongoing bipolar disease diagnosed approximately 10 years ago. Concomitant medication included duloxetine hydrochloride (CYMBALTA) 30mg tablet daily by mouth. She reported the instructions say to take white pills day 1-3 and two times a day on days 4-7. She only received blue pills and no white pills. The patient reported that she received the continuing box. Her physician told her to go ahead and start on the 1 mg dose. So she was started out on the 1 mg daily dose of varenicline as she did not get a starter pack just a continuing month pack. The patient started varenicline on the morning of 29Jan2015 with the 1mg blue pills (Lot: D10288530, Expiration: 21Jan2016, NDC: 0069-0469-11), and it made her sleepy on the same day. She lay down about noon and woke up at 1500 later that day. She stated that she had smoked half of two cigarettes on 29Jan2015 and she usually smoked a pack of cigarettes daily. The patient was no longer taking the product in 2015 (as of 06Feb2015). Her mouth became really dry and her tongue became stuck

	to the roof of her mouth while she was asleep (in 2015). Relevant laboratory tests were unknown. Therapeutic measures were not reported. The clinical outcome of 'sleep' was recovered on 29Jan2015, while 'mouth became really dry and her tongue became stuck to the roof of her mouth' was unknown. Follow-up (06Feb2015): New information reported from a non-clinical study program, Chantix CV Label Update Teleservices Scripts from a contactable female consumer includes: event data (added mouth became really dry and her tongue became stuck to the roof of her mouth while she was asleep) and action taken (permanently withdrawn). Follow-up (10Feb2015): This is a follow-up report combining information from duplicate reports 2015044752 and 2015045039. The current and all subsequent follow-up information will be reported under manufacturer report number 2015044752. New information reported from the same contactable consumer includes: suspect drug (added new posology, lot, Expiration Date and NDC), medical history, concomitant medication and reaction data (added 'sleepy' with outcome of recovered)
10864163	This is a spontaneous report from a non-clinical study program Chantix CV Label Update Teleservices Scripts from a contactable consumer. A 36-year old female patient of an unspecified ethnicity started to receive varenicline tartrate (CHANTIX) via an unspecified route of administration from Jan2013 at an unknown dose and frequency for an unspecified indication. The patient's medical history and concomitant medications were not reported. The patient stated she thought something wasn't right at the time, because it didn't work very well (Jan2013). As soon as she took one drag from her sister's cigarette, she restarted smoking. Patient stated she wanted to quit smoking again. She was currently getting back on it. She was having some medical issues, going through a divorce, and couldn't work out. She was given the starter pack that contains 0.5 mg tablets and 1 mg tablets. She realized she was not given the starter pack the first time, in Jan2013. She isn't certain of the dose, but she did not take a starter dose. The action taken in response to the events for varenicline tartrate was unknown. The clinical outcome of the events was unknown.
11094232	This is a spontaneous report from a non-clinical-study program, Chantix/Chantix CV label update teleservice script. A contactable 72-year-old Caucasian male consumer started to receive varenicline tartrate (CHANTIX) (LOT E10447930; expiration date Oct2017; NDC 3 0069046912 6) from Jun2014 at 1 mg once daily to quit smoking. Medical history included pancreatitis. The concomitant medications were not reported. The consumer had his experienced gall bladder removed in Feb2015 and hospitalized for about a week. The patient had been without varenicline tartrate at least 4 or 5 months in Aug2014. He stated that this was his third batch and he did not have white pills in the pack. Directions stated to take the white pills for the first 3 days and then 2 blue pills a day until finish. The patient just purchased the third batch of varenicline tartrate. This pack did not have the white pills in it. There were no white pills in the package. The patient stated that the physician just prescribed prescription for 2nd request instead of the original request which included the beginning white pills. Since he didn't get the white pills to start, he had to buy those separate. As far as he was concerned his doctor screwed up the prescription which caused him the additional expense of buying the white pills. Originally he quit on 25Jun2014, went for numerous months without smoking. He smoked 2-3 cigarettes lately. The urge to smoke was still there. The action taken in response to the event for varenicline tartrate was dose not changed. The outcome of the event gall bladder removal was recovered in Feb2015. Follow-up (29Jun2015): New information received from a contactable consumer includes: reaction data (new event my doctor screwed up the prescription).

	Follow-up attempts completed. No further information expected.
11219179	This is a spontaneous report from a non-contactable consumer. A male patient, of an unspecified age and ethnicity, started to receive varenicline tartrate (CHANTIX), dose unknown for an unspecified indication, beginning on an unspecified date. The patient's medical history was not reported. The patient's concomitant medications were not reported. The directions said to take the white pills before the blue pills but he did not have any white pills. He has been taking the blue pills and it made and it was making him "sick as hell", dizzy, was vomiting and he "pooped himself and just about anything one can't imagine coming out of it". The action taken with varenicline tartrate in response to the events was unknown. The outcome of the event was unknown. No follow up attempts possible. No further information expected.
11287619	The initial case was missing the following minimum criteria: No adverse effect. Upon receipt of follow-up information on 14Jul2015, this case now contains all required information to be considered valid. This is a spontaneous report from a contactable consumer. A 69-year-old, Caucasian, male patient started to receive oral varenicline (CHANTIX) for a while about 6 months ago (2015) at the starter dose and he quit smoking. He began again on varenicline tartrate from 31Mar2015 at 1 mg for stop smoking / quit smoking (expiration 24Mar2016). Medical history included back issues, back surgery from 1997 (11 back surgeries since 1997, Consumer stated he had back surgeries and one guy messed up so bad, his back had gotten so bad and was just about bed ridden); had put on weight; hypertension ongoing since his 40's, blood pressure was usually high; ongoing diabetes; ongoing high cholesterol since 1995; chronic infection ongoing since 15Nov2013 (he got the infection at the hospital after a surgery, type of surgery not specified, and had to wear a wound VAC for 4 months); acid reflux ongoing since 7 or 8 years ago; arthritis ongoing since 10-15 years ago, and chronic back pain from 1996 or 1997 (the patient can't walk or stand much because of chronic back condition), triple bypass 7 years ago, Type 2 diabetes, leukemia 8 years ago. Past drug events included hydrocodone/ acetaminophen (VICODIN) 5 mg in 1997 and acetaminophen/ hydrocodone (NORCO 5/325 mg strength (unknown start date) did not help his back pain. He was not currently taking hydrocodone/ acetaminophen. Previously, nicotine (NICORETTE GUM) and nicotine (NICODERM PATCH) did not work. On nicotine (NICODERM PATCH), his arms broke out and his hip broke out, patches made the arms itch like crazy, raw, and scab. Concomitant medications included pravastatin 40mg one tablet by mouth daily for high cholesterol; lisinopril 20mg one tablet by mouth daily for high blood pressure; omeprazole 20mg one capsule by mouth twice daily for acid reflux; metoprolol 25mg one tablet by mouth daily unknown indication but for his heart; glimepiride 4mg one tablet by mouth daily for diabetes and sugar control; metformin 1000mg one tablet by mouth daily for diabetes and sugar control; diclofenac sodium (DICLOFEN) 75mg one tablet by mouth twice daily for arthritis; doxycycline hydrochloride (DOXYCYCL) 100mg one capsule by mouth daily for chronic infection; hydrocodone bitartrate/ paracetamol (NORCO) 7.5/325mg tablets every 4-6 hours for back pain; and nicotine (NICORETTE). The consumer mentioned that he was taking varenicline tartrate for a while about 6 months ago (2015) and he quit smoking and started smoking again 4 months ago due to stress in 2015 with outcome of unknown. The consumer confirmed that he started smoking after stopping varenicline tartrate and he got varenicline tartrate again to quit smoking. It was not reported if he completed the first course of varenicline tartrate. When he started back on varenicline tartrate on 31Mar2015 he did not start with the starter kit, he started with the blue pill and he only took 3 of them. Then made it unclear as to when or how much medication was taken as he stated 6 pills were out of the package. He did not know why he started on the blue pill instead of the starter kit. The patient was in a coma for 3 days on

	01Apr2015 with outcome of recovered in 2015. The consumer stated he thought the patient made a mistake and he maybe took too many of them. The consumer stated the way it sounded the patient started with a higher dose. On 01Apr2015, although the consumer stated he was found unresponsive in his house, his wife got on the phone later and stated he was only found disoriented, confused, and out of it, he wasn't unresponsive. The consumer was hospitalized for these events on 01Apr2015 through 06Apr2015 with outcome of recovered on an unspecified date in 2015. Additionally, the consumer experienced carpal tunnel on 13Jul2015 with outcome of not recovere
11467997	This is a spontaneous report from non-clinical-study program (Chantix CV Label Update Teleservices Scripts) for a contactable consumer who reported for his wife. This consumer reported similar events for himself and his wife. This is second of two reports. A female patient of an unspecified age and ethnicity started to receive varenicline tartrate (CHANTIX), route of administration, date and dose unspecified to quit smoking. The medical history and concomitant medications were not reported. The patient stopped smoking with varenicline tartrate and then she started smoking again. The patient mentioned it did not do a very good job. The patient also reported she did not receive any of the white pills, 0.5 mg pills and mentioned he only got the 1.0 mg pills. The action taken in response to the events for varenicline tartrate was unknown. The outcome of the events was unknown.
11468079	This is a spontaneous report from a non-clinical-study program (Chantix CV Label Update Teleservices Scripts) for a contactable consumer. This consumer reported similar events for himself and his wife. This is the first of two reports. This male consumer of an unspecified age and ethnicity started to receive varenicline tartrate (CHANTIX), route of administration, date and dose unspecified to quit smoking. The medical history and concomitant medications were not reported. The consumer stopped smoking with varenicline tartrate and then he started smoking again. The consumer mentioned it did not do a very good job. The consumer also reported he did not receive any of the white pills, 0.5 mg pills and mentioned he only got the 1.0 mg pills. The action taken in response to the events for varenicline tartrate was unknown. The outcome of the events was unknown.
11487106	This is a spontaneous report from a consumer (patient's boyfriend). A 66-year-old Caucasian female patient started to receive varenicline tartrate (CHANTIX) via an unspecified route of administration at 1 mg from 01Sep2015 to 03Sep2015 to quit smoking. The patient medical history and concomitant medications were not reported. The patient opened the varenicline tartrate starter pack and accidently pushed the wrong pills out. For three days, she was taking the wrong pills. She was taking the blue 1mg pills instead of the white 0.5mg pills. The reporter just found out about it on 03Sep2015. The reporter told the patient to stop taking the varenicline tartrate because she started experiencing confusion on 03Sep2015. The patient was getting confused a lot and can't remember what happened yesterday or what they did since 03Sep2015. The reporter threw away the varenicline tartrate starter pack and patient will not be taking the varenicline tartrate again. The action taken for varenicline tartrate in response to the events was permanently withdrawn. Her last dose was taken on 03Sep2015 at 1 PM. The events "getting confused a lot" and "can't remember what or what they did" was ongoing but had improved after the varenicline tartrate was stopped. The outcome of events was "getting confused a lot" and "can't remember what or what they did" was recovering. The event "taking the blue 1mg pills instead of the white 0.5mg pills" was stopped on 03Sep2015.
11514012	This is a spontaneous report from a Pfizer-sponsored program Chantix CV Label

	Update Teleservices Scripts from a contactable consumer. A 70-year-old Caucasian female patient started to receive varenicline tartrate (CHANTIX) starter pack via an unspecified route of administration from 15Jul2015 at an unknown dose and frequency to quit smoking / stop smoking. Medical history included scleroderma, chronic obstructive pulmonary disease (COPD), diabetes and congestive heart failure which was under control. She stated that she only had one attack with it but it was an "old" attack. She added that COPD was the reason for which she wanted to quit smoking and that her husband died because of cigarettes and that was the wake-up call for her. Concomitant medications included atorvastatin calcium (LIPITOR), omeprazole, bumetanide, potassium chloride, calcium carbonate / colecalciferol (CALCIUM WITH VITAMIN D), magnesium, iron, and cetirizine hydrochloride (ZYRTEC), all ongoing. The patient mentioned that she started taking varenicline in July, around 15Jul2015. Her son picked up her prescription and she noticed that she did not have a starter box and they had given her a continuing box in 2015. She had to call them to tell that they had not given her the starter box. They told her that they would give it to her. They took two weeks to give the starter pack. She took the starter box and did well with it, it was working and she was having minimal side effects. From an unspecified date in 2015, she was having a little nausea after dinner pill but not after the morning pill. She was having vivid dreams but not frightening dreams, they were just crazy dreams but that was not affecting anything. She added that she took it for 3 weeks and that was when the trouble started. She was taking 1 mg, twice a day, one in the morning after breakfast and one in the evening after dinner. She was 2 days into the 3rd week and she got sick/very ill and the problems that she had were side effects, vomiting and nausea as it turned out. She quit taking the medication for a while because she thought that maybe it was due to the pill and to see if she could get better. She quit taking them but did not get better and as it turned, she had to have gall bladder surgery in a few weeks. She said they would be removing her gall bladder on 16Oct2015. She mentioned that nausea and vomiting were not from the Chantix, they were from her gall bladder. She then called her doctor to see if she could continue taking the varenicline. She thought that it had been over a month when she quit and she asked if she should start on the starter pack and start it all over. She had her continuing pack and she had completed her starter pack. She added that her doctor told her that she should not do that and should just pick up where she left off. The patient mentioned that she was not feeling sick but she had to have the surgery and would go back home and wait until after the surgery. The patient had admission to hospital involved and received treatment for had to have gall bladder surgery, sick/ got very ill and she did not have a starter box and they had given her a continuing box. The patient had surgery on 23Oct2015. The patient mentioned that she had not received any treatment for her other side effects. She added that her side effects were minimal and she had a little bit of nausea, little bit of dreaming and it was nothing that could concern her. The action taken in response to the events for varenicline tartrate was temporarily withdrawn in 2015. The clinical outcome of the event sick/ill, had to remove her gallbladder and she did not have a starter box and they had given her a continuing box was recovered in 2015, for vivid crazy dreams and nausea was recovering, of vomiting was unknown. Follow-up (20Nov2015): New information received from the contactable consumer includes: seriousness (hospitalization), treatment and event outcomes. Follow-up attempts completed. No further info
11650847	This is a spontaneous report from a Non-Clinical-Study program Chantix CV Label Update Tele-Services Script. A contactable female consumer of an unspecified age and ethnicity started to receive varenicline tartrate (CHANTIX), oral from an unspecified date at 1 mg to quit smoking. The patient medical history was not reported. The patient's concomitant medications were not reported. The patient

	previously took varenicline tartrate over 5 years ago, then stopped smoking very little and then went right back. The doctor did it wrong this time and gave her just the blue pills instead of the starter pack whites that you take first. She had them awhile and didn't know if she should take them or not. She had not taken them yet. Sticker label was ripped because she had it so long. The action taken in response to the event for varenicline tartrate was not applicable. The outcome of the event was unknown. She started varenicline on an unknown date and two weeks into use, still had the urge to smoke. Follow-up (01Apr2015): Follow-up attempts completed. No further information expected. Follow-up (15Oct2015): New information from a contactable consumer included: case details.
11779255	This is a spontaneous report from a Pfizer-sponsored program [Chantix CV Label Update Teleservices Scripts]. A contactable consumer reported for a 59-year-old Other White female patient started to receive varenicline tartrate (CHANTIX) from 2009 to 2010 at an unspecified dose and then from 14Nov2015 to 17Nov2015 cut the pills in half to quit smoking. Medical history included ongoing depression from 1995, ongoing insomnia from 1995, anxiety, diabetes, blood pressure abnormal. Concomitant medication included 3 different types of insulin, antidepressants, sleep medicine, and may be on blood pressure medicines. The patient previously took alprazolam (XANAX) for anxiety and it wasn't working. The first time the patient took varenicline tartrate was 2009 to 2010. The patient had quit smoking for a year after taking varenicline tartrate and started smoking again after either her mom or dad passed away. The patient started smoking because of the stress. She said, maybe it never took the craving away. the patient received a prescription for varenicline tartrate. When she picked it up it was the second pack, instead of the starter pack in 2015. When she contacted the doctor, the doctor told her to split the pills. The patient was very mean when on varenicline tartrate, and clarifies that this occurred during the first time she was on Chantix in 2009 to 2010. The patient underwent blood work and everything was fine. The action taken in response to the events for varenicline tartrate was permanently withdrawn. The outcome of the events was unknown.
11803717	This is a spontaneous report from a contactable consumer. A 62-year-old Caucasian female patient started to receive varenicline tartrate (CHANTIX), via an unspecified route of administration from an unknown date at a half of pill (she broke the 5 mg pill in half) for 1-3 days to stop smoking. Medical history included ongoing emphysema diagnosed five years ago, high cholesterol, diabetes from Jan2014 and ongoing, ongoing low potassium, ongoing underactive thyroid diagnosed three or four years ago, ongoing blood pressure high, osteoporosis, panic attack, anxiety, depression, gastrooesophageal reflux disease (GEOD) and liver (prophylaxis). Concomitant medications included metformin, thyroid, hydrochlorothiazide, potassium chloride, lovastatin, acetylsalicylic acid (BAYER ASPIRIN), esomeprazole magnesium (NEXIUM 24HR), vilazodone hydrochloride (VIIBRYD), alprazolam (XANAX), colecalciferol (VITAMIN D3), calcium, magnesium, beclometasone dipropionate (QVAR). The patient experienced cannot eat on an unspecified date, constipation on 24Nov2015, nausea on 21Oct2015. She has been having bad nausea since the first pill. She got the blue pills, did not get the white. She was a half of pill (she broke the 5 mg pill in half) for 1-3 days. The 5mg they told her to break in two and to take for 1 to 3 days. Then she took one tablet (5 mg) for 4-7 days, took one in morning and evening. Then day 8 to the end of treatment took one in the morning and one in the evening, which she was still doing, but stated she should have stopped by now. It said on here 30 to 35 days of treatment but she had not stopped smoking and had been smoking through the whole thing. In reference to whether she had stopped smoking, she had not stopped, she had slowed down a lot because it is making her so nauseous. It was making her so nauseous that she could barely eat, she was a

	Type 2 diabetic and had to eat 3 meals a day. She also had emphysema which was why she wanted to stop smoking. The product was not getting her off of the cigarettes, what was it going to take another 3 months. She went to the doctor because she was so sick and he gave her a pill to control the nausea. The doctor gave her medication to control the nausea, which she was not taking it because it caused constipation and she already has constipation from the varenicline. The action taken in response to the events for varenicline tartrate was dose not changed. Therapeutic measures were taken as a result of constipation. The outcome of the event constipation was recovered, of the other events was not recovered. Follow up (02Dec2015): New information reported from a contactable consumer includes: product data clarification.
11871850	Case received via Johnson & Johnson: This spontaneous report was received from a 69-years-old white male patient reporting on self via another company (Pfizer Inc. - 2015445363, US15-079554), from The United States: 2015445363. The patient's height was 175.0 centimeters and weight was 108.86 kilograms. The patient's medical history and concurrent conditions included, back surgery (had back surgeries and one guy messed up so bad), high blood pressure, leukemia (8 years ago), smoker, triple bypass (7 years ago), and type 2 diabetes. Patient reported that, his back had gotten so bad and was just about bed ridden. He states he had put on weight. His blood pressure was usually high. The patient was treated with nicotine (chewing gum, batch number and expiry date: unspecified, unspecified route of administration, dose and frequency) initiated on an unspecified date, for an unspecified indication. Non-company suspect drugs included, Varenicline tartrate (oral, tablet, batch number: unspecified, expiry date: 24-MAR-2016) 5.0 mg twice a day (1 tablet in the morning and 1 in the evening by mouth), initiated on an unspecified date, to quit smoking. Concomitant medications were not reported. On an unspecified date, patient reported that nicotine chewing gum did not help. It was reported that the patient was not taking Varenicline tartrate then but started smoking again. Patient's family doctor recommended Varenicline tartrate to him. Patient reported that, on 31-MAR-2015, he took one pill in the morning, one in the evening, and one the next morning of Varenicline tartrate. He went to the hospital to see his wife before she had surgery and went back home and he states his granddaughter found him on the floor. He had a seizure and was hospitalized for 3 days. He states he was in a coma, but described being in a coma as remembering seeing the hospital name and a male nurse coming into the room. He was in hospital from 01-APR-2015 to 04-APR-2015. The patient reported that, he took blue pill instead of doing the starter for two weeks of Varenicline tartrate. He believed that he went straight to taking 2 a day. The patient reported that, he started Varenicline tartrate on 31-MAR-2015 and stopped on 01-APR-2015, but then made it unclear as to when or how much medication was taken as he states 6 pills are out of the package. He had 3 blue packages and 1 yellow. Action taken with nicotine chewing gum was not reported and treatment with Varenicline tartrate was withdrawn on an unspecified date. Outcome of event did not help was not reported. This report was associated with product complaint and product complaint number was not reported. This report was not serious. This case, involving the same patient is linked to 20151216793. Additional Information: Reporter causality assessment - The causal relationship between the events and suspect product was considered to be possibly related. Licensing Partner causality assessment - The causal relationship between the events and suspect product was considered to be possibly related
11883381	This is a spontaneous report from a contactable consumer. A 32-year old Black male patient started to receive varenicline tartrate (CHANTIX) starter pack oral from

	Oct2015 at an unknown dose and frequency to stop smoking which was increased to 1 mg twice a day on an unspecified date in 2015. The patient's medical history and concomitant medications were not reported. The patient experienced feeling funny, felt disoriented, felt really depressed, and having dreams in 2015. The dreams began the first week of taking varenicline. He could tolerate the dreams. He would have 15 to 20 dreams a night. He stated that they were kind of interesting and weren't nightmares or anything. Feeling funny, disoriented, and really depressed began the third week after starting varenicline. The patient felt the product was helping him to quit smoking; he just couldn't take the way he was feeling. He could fight the urges easier while on varenicline. He stopped taking the 1 mg product a week ago, on 18Dec2015, because he was feeling funny. This was a temporary stop. The symptoms went away when he stopped the varenicline. He wanted to start taking the product again. The patient stated his doctor accidently gave him the starting pack twice. That is why he has it available now. The action taken in response to the events for varenicline tartrate was temporarily withdrawn on 18Dec2015. The clinical outcome of the events was recovered in Dec2015.

E.4 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

APPENDIX F. N/A

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[7] along with postmarket medication error data, we reviewed the following Chantix labels and labeling submitted by Pfizer, Inc. on October 13, 2015.

- Medication Guide

G.2 Label and Labeling Images

(b) (4)

[7] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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

---

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

/s/

MILLIE C BRAHMBHATT
03/18/2016

BRENDA V BORDERS-HEMPHILL
03/18/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021928/S-039

RISK MITIGATION and RISK ASSESSMENT REVIEW(S)

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

Risk Evaluation and Mitigation Strategy (REMS) Addendum Review

Date:	August 12, 2016
Reviewer/Team Leader:	Kimberly Lehrfeld, Pharm.D. Division of Risk Management
Division Director:	Cynthia LaCivita, Pharm.D. Division of Risk Management
Drug Name:	Chantix (varenicline)
Therapeutic Class:	Smoking cessation agent
Dosage Form:	Tablet
Application Type/Number:	NDA 21928
Supplement Number:	Prior Approval Supplement 039 and 041
Applicant/sponsor:	Pfizer, Inc.
OSE RCM #:	RCM # 2015-2499; 2015-2501

*** This document contains proprietary and confidential information that should not be released to the public. ***

The purpose of this addendum review is to update the Division of Risk Management's (DRISK) evaluation of the proposed modification to the risk evaluation and mitigation strategy (REMS) for Chantix (varenicline) tablets, NDA 21928.

On July 15, 2016, the Division of Analgesia, Anesthesia and Addiction Products (DAAAP) issued a safety label change (SLC) letter to Pfizer requiring the addition of the risk of somnambulism to the Chantix (vaenicline) tablets US Prescribing Information (USPI) and Medication Guide (MG). These label changes were submitted on August 2, 2016 to both Prior Approval Supplement (PAS) 41 and PAS 39 (eCTD Sequence No. 403).

This addendum updates the Division of Risk Management's (DRISK's) review of PAS 039 (D Gonzalez, DRISK REMS Review, June 14, 2016) and confirms that the SLC changes to the Chantix USPI and MG required by the Agency on July 27, 2016 do not impact the Chantix REMS document or REMS Supporting document which were submitted on October 13, 2015, as part of PAS 039. The revised USPI and MG, as stipulated by DAAAP in the SLC letter (dated July 15, 2016) that was submitted by Pfizer on August 2, 2016 will be reviewed by DAAAP.

DRISK finds the REMS for Chantix, NDA 21928, as appended to DRISK's review dated June 14, 2016 (D Gonzalez) acceptable for approval.

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

/s/

KIMBERLY LEHRFELD
08/12/2016

CYNTHIA L LACIVITA
08/12/2016
concur

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

Risk Evaluation and Mitigation Strategy (REMS) Review

Date:	June 14, 2016
Reviewer:	Danny S. Gonzalez, Pharm.D., M.S. Division of Risk Management
Team Leader:	Kimberly Lehrfeld, Pharm.D. Division of Risk Management
Division Director:	Cynthia LaCivita, Pharm.D. Division of Risk Management
Drug Name(s):	Chantix (varenicline)
Therapeutic Class:	Smoking cessation agent
Dosage Form:	Tablet
Application Type/Number:	NDA 21928
Applicant/sponsor:	Pfizer, Inc.
OSE RCM #:	RCM # 2015-2499; 2015-2501

*** This document contains proprietary and confidential information that should not be released to the public. ***

1 INTRODUCTION

The purpose of this review is to document the Division of Risk Management's (DRISK) evaluation of the proposed modification to the risk evaluation and mitigation strategy (REMS) for Chantix (varenicline) tablets, NDA 21928. The proposed modifications to the REMS were submitted by Pfizer on October 13, 2015, as part of a Prior Approval Supplement (PAS) (S-039).

The supplement proposes revisions to the U.S. Prescribing Information (USPI) and the Medication Guide (MG) based on varenicline clinical data in smokers who were not willing or able to make an abrupt quit attempt, but who were willing to reduce their smoking with the ultimate goal of quitting. The sponsor's proposal includes a new dosing regimen in the USPI and MG.

The Sponsor did not propose any changes to the Chantix REMS Document. The changes to the MG were reviewed by the Division of Medical Policy, Patient Labeling Team (PLT) under separate cover, and were found to be acceptable.

1.1 BACKGROUND

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

Chantix was originally approved on May 10, 2006 and is indicated for use as an aid to smoking cessation treatment. Chantix is available in 0.5 mg and 1 mg capsules. Chantix dosing should begin one week before the date set by the patient to stop smoking or alternatively, the patient can begin dosing, and then quit smoking between days 8 and 35 of treatment. The starting week dose is 0.5 mg once daily on days 1-3 and 0.5 mg twice daily on days 4-7. For continuing weeks of treatment, the dosing is 1 mg twice daily for a total of 12 weeks. An additional 12 weeks of treatment is recommended for successful quitters to increase likelihood of long-term abstinence.

Chantix was originally approved on May 10, 2006 without a REMS. On May 16, 2008, in addition to the approval of a MG for Chantix, the Agency communicated to the Sponsor that under Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA), a REMS should be submitted. The Agency cited that "since Chantix was approved on May 10, 2006, as an aid to smoking cessation treatment, we have become aware of post-marketing reports of neuropsychiatric symptoms, including changes in behavior, agitation, depressed mood, and suicidal thoughts or actions associated with Chantix. This information was not available when Chantix was granted marketing authorization as an aid to smoking cessation treatment. Therefore, we consider this information to be "new safety information" as defined in FDAAA."

The Chantix REMS was approved on October 19, 2009. The goal of the REMS was "to inform patients about the serious risks associated with the use of Chantix, including the potential risk of serious neuropsychiatric symptoms in patients taking Chantix". The

REMS elements include a MG and a timetable for submission of assessments (18 months, 3- and 7-years after approval).

Approved REMS modifications for Chantix are included in section 1.2 Regulatory History.

1.2 REGULATORY HISTORY

April 22, 2010: Revisions to the MG "Who should not take Chantix" section were included in a REMS modification.

July 22, 2011: Revisions to the MG to include new information about how to take Chantix and possible side effects were included in a REMS modification.

September 19, 2014: A REMS modification was approved to include changes to the U.S. Prescribing Information (USPI) and MG based on postmarketing data that resulted in safety labeling changes about interaction with alcohol and Chantix, reported cases of seizures with Chantix use, along with a revision to the Chantix REMS goal statement to read "The goal of this REMS is to inform patients about the potential serious risk of neuropsychiatric adverse events associated with the use of Chantix".[1]

October 13, 2015: The Sponsor submitted an efficacy supplement which proposes to add an additional dosing regimen with a gradual approach to quitting smoking for patients who are not able or willing to quit abruptly. The new regimen proposes patients begin Chantix and reduce smoking during the first 12 weeks of treatment, then quit by the end of that period and continue treatment for an additional 12 weeks for a total of 24 weeks.

2 MATERIALS REVIEWED

2.1 SUBMISSIONS

- Pfizer, Inc. Submission for Chantix (NDA 21928) dated October 13, 2015 (S-039; eCTD Sequence No. 0342)

2.2 OTHER MATERIALS INFORMING OUR REVIEW

- Mills S. Division of Labeling Review. Labeling review for Chantix (NDA 21928) dated May 27, 2016

3 PROPOSED REMS MODIFICATIONS AND RATIONALE

The Sponsor's REMS submission did not propose changes to the REMS document or REMS Supporting Document. The only changes were to the MG (see section 3.2.1).

3.1 REMS GOALS

This supplement did not include any changes to the Chantix REMS goal.

3.2. REMS ELEMENTS

3.2.1. MEDICATION GUIDE

The proposed revisions to the Chantix MG include addition of language to the "How Should I Take Chantix" section of the MG reflecting the newly proposed dosing regimen for Chantix.

Reviewer comments: The Office of Prescription Drug Promotion (OPDP)/Patient Labeling Review Team's (PLRT) reviewed the Sponsor's proposed Chantix Medication Guide (MG) under separate cover and has communicated their recommendations to DAAAP. OPDP/PLRT has found the MG submission to be acceptable with their recommended changes. (see section 2.2).

4 DISCUSSION AND CONCLUSION

The attached REMS for Chantix (NDA 21928), originally submitted on October 13, 2015, aligns with the currently approved Chantix REMS, which is required to inform patients about the potential serious risk of neuropsychiatric adverse events associated with the use of Chantix.

5 RECOMMENDATIONS

DRISK recommends approval of the REMS for Chantix, NDA 21928, as appended to this review.

ATTACHMENT:

REMS Document submitted by Sponsor on October13, 2015

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/

KIMBERLY LEHRFELD
06/14/2016

CYNTHIA L LACIVITA
06/14/2016
Concur

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021928/S-039

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 021928/S-039

ACKNOWLEDGMENT --
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)/pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 021928

SUPPLEMENT NUMBER: S-039

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

DATE OF SUBMISSION: October 13, 2015

DATE OF RECEIPT: October 13, 2015

This supplemental application proposes the following changes to the Package Insert based on clinical trial data from the study titled, "A Phase 4, Multi-National, Randomized, Double-Blind, Placebo- Controlled Study to Evaluate the Efficacy and Safety of Varenicline Compared to Placebo for Smoking Cessation Through Reduction" and modifications to the approved risk evaluation and mitigation strategy (REMS) for Chantix which include revisions to the Medication Guide.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on December 12, 2015, in accordance with 21 CFR 314.101(a).

If the application is filed, the goal date will be August 12, 2015.

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. 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).

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 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
10/20/2015