CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

021928Orig1s041

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-041

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	
Medical Review(s)	
Chemistry Review(s)	
Environmental Assessment	
Pharmacology Review(s)	
Statistical Review(s)	
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-041

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-041

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

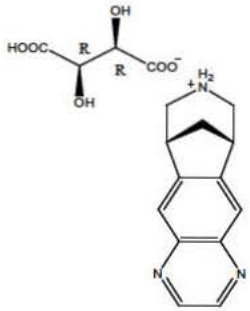
In case of overdose, standard supportive measures should be instituted as required.

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

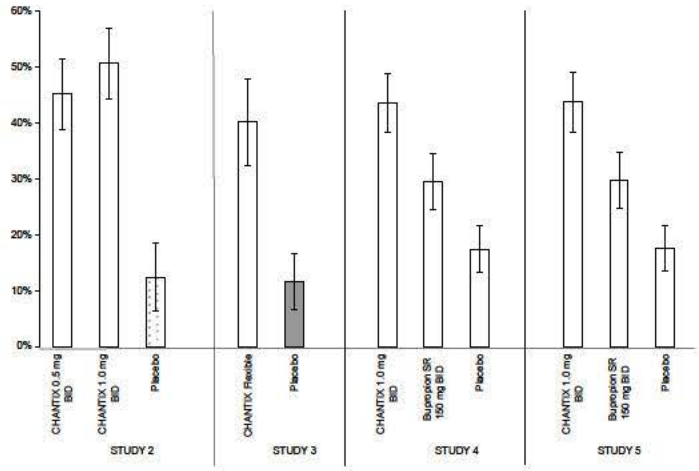


Table 6: Continuous Abstinence, Weeks 9 through 12 (95% confidence interval)

	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

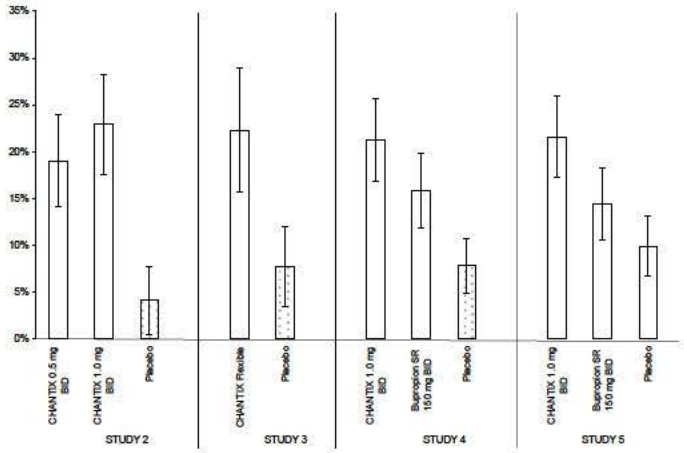


Table 7: Continuous Abstinence, Weeks 9 through 52 (95% confidence interval) Across Different Studies

	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

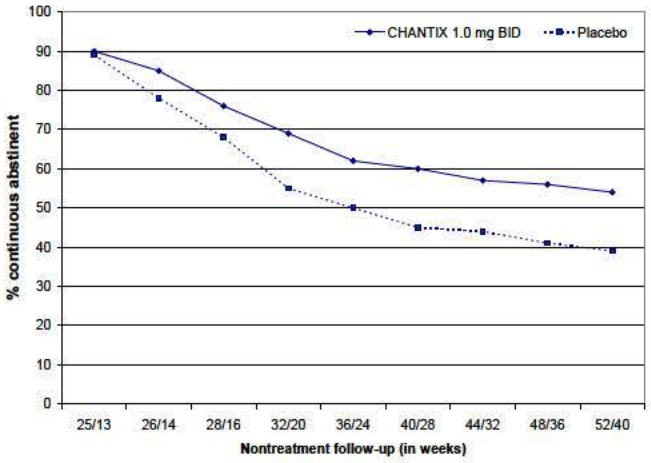
Study 6

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-041

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-041

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-041

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021928/S-041

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021928/S-041

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

From: Augustus, Ayanna
To: Donohew, Lilya
Cc: Augustus, Ayanna
Subject: RE: Section 901 Safety Labeling Change/Revised Labeling
Date: Wednesday, July 27, 2016 10:09:02 AM
Attachments: Chantix somnambulism SLC and RTQ 07 26 16.doc

Hi Lilya,

Attached is the Division's revised labeling. Please review and provided a response, via email, by Monday, August 1st. If you have no additional revisions the label please submit the clean and tracked labeling to the SLC supplement and S-039 as soon as possible.

Thanks,
Ayanna

Ayanna Augustus, PhD, RAC
Sr. Regulatory Health Project Manager
FDA/CDER/OND/ODEII/DAAAP
Fax: 301-796-9723
Ph: 301-796-3980

24 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
07/27/2016