CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

021928Orig1s011

Trade Name: CHANTIX

Generic or Proper Name: varenicline tartrate

Sponsor: Pfizer, Inc.

Approval Date: 10/19/2009

Indication: CHANTIX is indicated as an aid to smoking cessation treatment.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021928/S-011

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021928/S-011

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021928/S-011

APPROVAL LETTER

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

Attention: Lilya I. Donohew, Ph.D.
Director, Worldwide Regulatory Affairs

Dear Dr. Donohew:

Please refer to your supplemental new drug application dated September 5, 2008, received September 5, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Chantix (varenicline) Tablets 0.5 mg and 1 mg.

We acknowledge receipt of your submissions dated April 30 and July 15, 2009.

This supplemental new drug application provides for a Risk Evaluation and Mitigation Strategy (REMS) for Chantix (varenicline). The REMS consists of a Medication Guide and a timetable for submission of assessments of the REMS.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a REMS if FDA becomes aware of new safety information and makes a determination that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)).

Since Chantix (varenicline) was approved on May 10, 2006, we have become aware of postmarketing reports of neuropsychiatric symptoms, including changes in behavior, agitation, depressed mood, and suicidal thoughts or actions associated with Chantix (varenicline). This information was not available when Chantix (varenicline) was granted marketing authorization as an aid to smoking cessation treatment. We consider this information to be "new safety information" as defined in FDAAA.

Your revised proposed REMS, submitted on July 15, 2009 and appended to this letter, is approved. The REMS consists of the Medication Guide included with this letter and the timetable for submission of assessments of the REMS.

Your assessment of the REMS should include an evaluation of patients' understanding of the serious risks of Chantix.

The requirements for assessments of an approved REMS under section 505-1(g)(3) include, in section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. You can

satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in 505-1(g) could result in enforcement action.

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

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:

NDA 021928 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 021928
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

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

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

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Ayanna Augustus, Regulatory Project Manager, at ayanna.augustus@fda.hhs.gov or (301) 796-3980.

Sincerely,

{See appended electronic signature page}

Bob A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia, and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:

1. REMS
2. Medication Guide

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21928	SUPPL-11	PFIZER INC	CHANTIX

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

/s/

BOB A RAPPAPORT
10/19/2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021928/S-011

LABELING

MEDICATION GUIDE

CHANTIX®

(varenicline) Tablets

Read the Medication Guide that comes with CHANTIX before you start taking it and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your condition or treatment.

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

Some people have had changes in behavior, hostility, agitation, depressed mood, and suicidal thoughts or actions while using CHANTIX to help them quit smoking. Some people had these symptoms when they began taking CHANTIX, and others developed them after several weeks of treatment or after stopping CHANTIX.

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

- 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.

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.

See "**What are the possible side effects of CHANTIX?**"

Some people can have allergic reactions to CHANTIX. Some of these allergic reactions can be life-threatening and include: swelling of the face, mouth, and throat that can cause trouble breathing. If you have these symptoms, stop taking CHANTIX and get medical attention right away.

Some people can have serious skin reactions while taking CHANTIX. These can include rash, swelling, redness, and peeling of the skin. Some of these reactions can become life-threatening. If you have a rash with peeling skin or blisters in your mouth, stop taking CHANTIX and see your doctor right away.

What is CHANTIX?

CHANTIX is a prescription medicine to help adults 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.

CHANTIX is not recommended for people under 18 years of age.

CHANTIX has not been studied with other treatments for stopping smoking.

What should I tell my doctor before taking CHANTIX?

Tell your doctor about all of your medical conditions including if you:

- have ever had depression or other mental health problems. See "What is the most important information I should know about CHANTIX?"

- have kidney problems or get kidney dialysis. Your doctor may prescribe a lower dose of CHANTIX for you.
- have any allergies. See the end of this Medication Guide for a complete list of ingredients in CHANTIX.
- are pregnant or plan to become pregnant. CHANTIX has not been studied in pregnant women. It is not known if CHANTIX will harm your unborn baby. It is best to stop smoking before you get pregnant.
- are breastfeeding. Although it was not studied in humans, CHANTIX may pass into breast milk. You and your doctor should talk about the best way to feed your baby if you take CHANTIX.

Tell your doctor about all your other medicines including prescription and nonprescription medicines, vitamins and herbal supplements. Especially, tell your doctor if you take:

- insulin
- asthma medicines
- blood thinners.

When you stop smoking, there may be a change in how these and other medicines work for you.

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?

- Take CHANTIX exactly as prescribed by your doctor.

1. Choose a **quit date** when you will stop smoking.
2. Start taking CHANTIX 1 week (7 days) before your **quit date**. This lets CHANTIX build up in your body. You can keep smoking during this time. Make

sure that you try and 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.

3. Take CHANTIX after eating and with a full glass (8 ounces) of water.
4. 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.

- 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.

Day 1 to Day 3	• White tablet (0.5 mg) • Take 1 tablet each day
Day 4 to Day 7	• White tablet (0.5 mg) • Take 1 in the morning and 1 in the evening
Day 8 to end of treatment	• Blue tablet (1 mg) • Take 1 in the morning and 1 in the evening

- 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 close to the time for your next dose, wait. Just take your next dose at your regular dose.

What should I avoid while taking CHANTIX?

Use caution driving or operating machinery until you know how CHANTIX may affect you. Some people who use CHANTIX may feel sleepy, dizzy, or have trouble concentrating, that can make it hard to drive or perform other activities safely.

What are the possible side effects of CHANTIX?

- **Some patients have had new or worse mental health problems.** See “What is

the most important information I should know about CHANTIX?"

- 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, 59 to 86°F (15 to 30°C).
- Safely dispose of CHANTIX that is out of date or no longer needed.
- **Keep CHANTIX and all medicines out of the reach of children.**

General information about CHANTIX

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

This Medication Guide summarizes the most important information about CHANTIX. 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 about CHANTIX and tips on how to quit smoking, go to **www.CHANTIX.com**

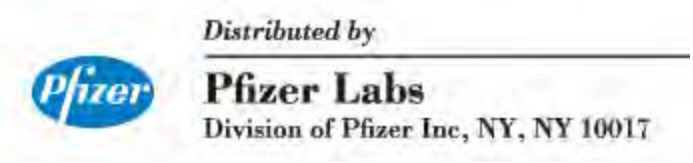
Or call **1-877-CHANTIX (877-242-6849)**.

What are the ingredients in CHANTIX?

Active ingredient: varenicline tartrate

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

Rx only



LAB-0328-8.0

Revised July 2009

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021928/S-011

REMS

NDA 021928 CHANTIX (varenicline) Tablets

Smoking Cessation

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

I. GOAL

To mitigate the potential risk of serious neuropsychiatric symptoms in patients taking Chantix by training patients about appropriate monitoring for psychiatric symptoms unusual to the individual, such as agitation, depressed mood and changes in behavior or if the patient develops suicidal ideation and suicidal behavior.

II. REMS ELEMENTS

A. Medication Guide

Pfizer will provide Medication Guides to pharmacists to be given to patients each time Chantix is dispensed to increase patient knowledge of how to safely and effectively use Chantix. Pfizer must provide copies of the Medication Guide for each unit of use bottle. Pfizer will make tear pads containing the Medication Guide available in pharmacies for direct distribution to patients.

B. Timetable for Assessments

REMS Assessments will be submitted to FDA 18 months, 3 years, and 7 years following REMS approval. 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 will submit each assessment so that it will be received by the FDA on or before the due date.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021928/S-011

MEDICAL REVIEW(S)

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND RHEUMATOLOGY PRODUCTS
HFD-170, 10903 New Hampshire Avenue, Silver Spring MD 20993
Tel: (301) 796-2280

Medical Officer Review

NDA: 21-928
Drug Name: Chantix
Applicant: Pfizer
Type of Submission: Supplement Labeling Request (SLR (b) (4), 012 and 013)
Date of Submission: (b) (4); January 16, March 19; April 30 of 2009
Date of Review: June 15, 2009
Reviewer: Anjelina Pokrovnichka, M.D.
Team Leader: Celia Winchell, M.D.
Project Manager: Ayanna Augustus

Table of Contents

1. Background

Chantix® contains the active ingredient, varenicline (as the tartrate salt), which is a partial agonist selective for $\alpha 4\beta 2$ nicotinic acetylcholine receptor subtypes. It was approved in May 2006 as an aid to smoking cessation treatment.

The Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP), in collaboration with the Office of Surveillance and Epidemiology (OSE), has been actively monitoring Chantix-related post-marketing adverse events reports to Adverse Event Reporting System (AERS). Based on this monitoring, the neuropsychiatric events (suicidality-related and non-suicidality-related) and the non-neuropsychiatric events of angioedema, serious cutaneous reactions, and accidental injuries were identified as safety concerns. This triggered a discussion for product label changes between the sponsor and the Division.

This review covers the following submissions and correspondence with the sponsor:

- [redacted] (b) (4)
- SLR 012 (January 16, 2009 submission)
- SLR 013 (March 19, 2009 submission)
- Sponsor's proposed label modifications (April 30, 2009)
- [redacted] (b) (4)
- Division's request letter concerning the suicidality-related events (February 19, 2009)

Contributions to the labeling recommendations in this review were made by the following individuals who provided reviews of individual safety issues and/or actively participated in the review process.

- OSE reviews:
  - Martin Pollock, Pharm. D. and Joann H. Lee, Pharm. D. – Review of postmarketing suicidality events (July 16, 2008)
  - Joann H. Lee, Pharm.D. – Review of postmarketing angioedema and serious skin reactions (October 30, 2008)
  - Martin Pollock, Pharm. D. – Review of postmarketing accidental injuries (October 30, 2008)
  - Martin Pollock, Pharm. D. – Review of postmarketing non-suicidal psychiatric events (December 8, 2008)
  - Jody Duckhorn--Division of Risk Management/OSE – Review of the Medication Guide (May 12, 2009)

- DDMAC review (May 5, 2009):
  - Mathilda Fienkeng-Regulatory Review Officer/DDMAC
  - Twyla Thompson-Regulatory Review Officer/DDMAC

It is also to note that where possible and appropriate, effort was made to create consistency with the Buproprione label (Zyban), another smoking cessation product that is also an antidepressant, when describing the neuropsychiatric symptoms.

The proposed changes for the Chantix label described in this review may not be final. Nevertheless, if any additional minor changes are allowed, they could be of editorial nature only without changing the meaning of the information that is being conveyed to the reader of the label.

2. Proposed Label Changes

The body of the review is structured to cover the labeling revisions in the following sequence:

1. Product label changes related to neuropsychiatric events.
2. Product label changes related to hypersensitivity reactions and angioedema.

3. Product label changes related to accidental injuries.
4. Product label changes related to serious skin reactions and the OSE AERS database analysis for these events.
5. Medication Guide changes.
6. Dear Healthcare Professional (DHCP) Letter changes.

2.1. Neuropsychiatric events.

In July, 2008 OSE performed a review of all suicidality-related events associated with Chantix from the AERS database. A conclusion was made that there was a close temporal relationship between the event and the drug use, and in many cases suicidality-related events occurred in patients without any known psychiatric history. This information was not available when Chantix was granted marketing authorization.

The sponsor was informed that the analysis conducted by OSE of available data constitutes *new safety information* within the meaning of Food and Drug Administration Amendments Act of 2007 (FDAAA) and that in accordance with section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act (FDCA), the new safety information should be included in the labeling for Chantix. On February 19, 2009, the Division issued a supplement letter, requesting that the suicidality-related events are highlighted in a boxed warning and additionally are appropriately described in the WARNINGS and ADVERSE REACTIONS sections of the product label.

Changes to the product label, addressing recommendations made by OSE (December 8, 2008 review) with regards to psychiatric events not including suicide, were also made. OSE had identified many types of psychiatric symptoms observed in post-marketing case reports, such as homicidal ideation, paranoia, psychosis, hallucinations, and aggression, which are important to include in labeling. However, to maintain the focus on the most serious concern, suicide, in the boxed warning, this information was added to a re-written version of the text in the main WARNINGS section, rather than in the boxed warning text. These concepts have also been included in the Medication Guide.

It is to note that after an internal discussion, a decision was made at a high Center-level management, to allow an inclusion of a statement in the boxed warning regarding the benefits of smoking cessation. Although viewed as potentially promotional by DDMAC, this statement has been added in the hope of preventing patients and prescribers from being deterred from making attempts to quit smoking, either with or without pharmacologic treatment. The health risks of smoking and the benefits of quitting are known to be substantial.

Taking into account the OSE and DDMAC recommendations, and the sponsor's proposed modifications, I recommend that the neuropsychiatric events are highlighted in a **boxed warning** and additionally described in the **WARNINGS** and **ADVERSE REACTIONS** sections of the product label using the following language:

- **Boxed warning**

WARNING:

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 post-marketing 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; some have experienced worsening of their psychiatric illnesses. Patients with serious psychiatric illness such as schizophrenia, bipolar disorder, and major depressive disorder did not participate in the pre-marketing studies of CHANTIX and the safety and efficacy of CHANTIX in such patients has not been established.

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 thinking or behavior that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behavior. In many post-marketing 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/Neuropsychiatric Symptoms and Suicide Risk, PRECAUTIONS/Information for Patients, and ADVERSE REACTIONS/Post-Marketing Experience**)

- **WARNINGS**

Neuropsychiatric Symptoms and Suicide Risk

Serious neuropsychiatric symptoms have been reported in patients being treated with CHANTIX (See **Boxed Warning, PRECAUTIONS/Information for patients, and ADVERSE REACTIONS/Post-**Marketing Experience) These post-marketing 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 pre-marketing studies of CHANTIX and the safety and efficacy of CHANTIX in such patients has not been established.

Advise patients and caregivers that the patient should stop taking CHANTIX and contact a health care 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 post-marketing 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.

- **ADVERSE REACTIONS**

Post-Marketing Experience
There have been reports of depression, mania, psychosis, hallucinations, paranoia, delusions, homicidal ideation, aggression, 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/Neuropsychiatric Symptoms and Suicide Risk, PRECAUTIONS/Information for Patients)**. 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.

2.2. Hypersensitivity reactions and angioedema.

(b) (4)

[redacted]

In October 2008 OSE consult provided review of the reported angioedema cases associated with Chantix therapy. In summary, as of 6/19/08, the AERS database contained 176 serious domestic cases of angioedema associated with varenicline. Specific symptoms reported were swelling of the mouth (n=107), with tongue being the most common (n=65). Sixteen cases reported swelling of the throat. Twenty (11%) cases reported that varenicline was the only contributing factor in the onset of the swelling events. A total of 26 (15%) cases required urgent medical attention. In five cases, respiratory compromise was documented. One patient required intubation for airway protection. The reported outcomes were hospitalization (13), life threatening (2), and other (171). In 55 (31%) cases positive dechallenge was reported.

Based on these data, the OSE recommended further strengthening of the language and the use of the term *life-threatening event* for the description of the angioedema.

Taking into account the OSE and DDMAC recommendations, and the sponsor's proposed modifications, I recommend that the hypersensitivity reactions, including angioedema are described in the **WARNINGS, PRECAUTIONS**/Information for patients and **ADVERSE REACTIONS** sections of the product label using the following language:

- **WARNINGS – Angioedema and hypersensitivity reactions.**

There have been post-marketing reports of hypersensitivity reactions including angioedema in patients treated with CHANTIX (See **ADVERSE REACTIONS/Post-Marketing Experience**). 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. Patients should be instructed to discontinue CHANTIX and immediately seek medical care if they experience these symptoms.

- **PRECAUTIONS – Information for patients.** *[additional bulleted item]*

Patients should be informed 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. Patients should be instructed to discontinue CHANTIX and immediately seek medical care if they experience these symptoms.

- **ADVERSE REACTIONS – Postmarketing Experience.**

There have been reports of hypersensitivity reactions, including angioedema (See **WARNINGS** and **PRECAUTIONS**).

2.3. Accidental injuries.

The December 2008 supplement request letter, in addition to the request for a stronger warning language for the angioedema, asked for adding information for accidental injuries and linking them to the adverse events of sleepiness, dizziness, loss of consciousness, and difficulty concentrating.

This request was primarily based on the findings of analysis performed by OSE that included the Chantix U.S. AERS reports from marketing until 10/17/08 for automobile accidents/injuries and associated events that at the time of the accident could have contributed to it by causing impairment of driving ability. This was performed in response to the ISMP publication (Quarter Watch: 2008 Quarter 1) where accidents and injuries were mentioned with varenicline use. Fifty-one of 63 reports were included in the case series. The OSE reviewer, Martin Pollock, found that for 39 cases the impairing event(s) occurred at or around the same time of the automobile accident. The most common events are listed below. One of them was loss of consciousness (n=7).

Contributing event	n
Anxiety-related	12
Abnormal behavior and or feeling abnormal	11
Memory impairment	10
Visual disturbance	9
Dizziness-related	8
Loss of consciousness	7
Aggression-related	7
Somnolence-related	7

Review of the narratives showed that for some cases subjects clearly related the preceding event of altered alertness and consciousness to the accidental injury/ automobile accident.

Therefore, the Division requested that this information is included in the **PRECAUTION** section of the label with language that clearly describes the association of the reported automobile accidents with events causing impairment of the driving ability, in particular, somnolence, dizziness, loss of consciousness and difficulty concentrating.

After negotiations with the sponsor, agreement was reached for the following language describing the accidental injuries:

- **PRECAUTIONS - Accidental Injury**

There have been post-marketing 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. Patients should be advised to use caution driving or operating machinery or engaging in other potentially hazardous activities until they know how CHANTIX may affect them.

2.4. Serious skin reactions.

The October of 2008 OSE review describes that as of 6/19/2008, the AERS database contained 10 unique serious U.S. cases of serious skin reactions. The reported events were Stevens Johnson Syndrome (5), Erythema Multiforme (4), and Exfoliative Dermatitis (1); there were no cases of toxic epidermal necrolysis. In two cases (2/10), tetracycline (labeled for Exfoliative Dermatitis) and amlodipine (labeled for Erythema Multiforme) were reported as co-suspect drugs. Two cases reported a positive dechallenge. The reported outcomes were hospitalization (2) and other (9). Eight cases were diagnosed by a physician with four confirmed by a dermatologist.

Table 5. Demographics and other characteristics of serious domestic AERS cases of serious skin reactions associated with varenicline, as of 6/19/2008 (N=10)	
Gender	Male (2), Female (7), Unknown (1)
Age in years (n=6)	Mean (49), Median (51), Range (34-62)
Indication	Smoking Cessation (7) Unknown (3)
Dose	Within normal dose Yes (7) No (0) Unknown (3)
Event (Serious Skin Reactions) (n=10)	Stevens Johnson Syndrome (5) Erythema Multiforme (4) Exfoliative Dermatitis (1)
Time to onset from start of therapy (n=6)	Mean (12 days), Median (13 days), Range (8-18 days)
Outcome	Hospitalization (2), Other (9)
Recovery	Yes (2), No (1), Unknown (7)
Dechallenge (n=3)	Positive (2), Unknown (1)

Received treatment for event	Yes (5) Steroids (n=3) Antihistamine (n=3) Aquaphor (n=1) No (0) Unknown (5)
Reporter	Physician (6), Pharmacist (1), Nurse (1), Consumer (2)
Report Type	Expedited 15-day (7), Direct (3)
Year Received	2007 (9), 2008 (1)

Serious skin reactions are currently not labeled.

Steven Johnson Syndrome is a dermatological emergency that if untreated can be fatal. Although, there were a small number of cases, the five SJS cases were reported by a physician and the relation to Chantix was clearly identified. Therefore I recommend that the seriousness of the skin reactions observed with Chantix therapy and the importance of timely medical evaluation are conveyed to the reader of the label. This information should also be reflected in the Medication Guide.

Taking into account the OSE and DDMAC input, I recommend that the serious skin reactions are included in the **WARNINGS**, **PRECAUTIONS** and **ADVERSE REACTIONS** sections of the label and described using the following language:

- **WARNINGS - Serious Skin Reactions** *[insert after **Angioedema and hypersensitivity reactions** subsection]*

There have been post-marketing reports of rare but serious skin reactions, including Stevens- Johnson Syndrome and Erythema Multiforme in patients using CHANTIX (See **ADVERSE REACTIONS/Post-Marketing Experience**) As these skin reactions can be life-threatening, patients should be instructed to stop taking CHANTIX and contact their healthcare provider immediately at the first appearance of a skin rash with mucosal lesions or any other signs of hypersensitivity.

- **PRECAUTIONS – Information for Patients** *[additional bulleted item]*

Patients should be informed that serious skin reactions, such as Stevens Johnson Syndrome and Erythema Multiforme, were reported by some patients taking CHANTIX. They should be advised to stop taking CHANTIX at the first sign of rash with mucosal lesions or skin reaction and contact a health care provider immediately.

- **ADVERSE REACTIONS- Postmarketing Experience** *[insert at the end of this subsection]*

There have also been reports of serious skin reactions, including Stevens Johnson Syndrome and Erythema Multiforme in patients taking CHANTIX (See **WARNINGS** and **PRECAUTIONS**).

2.5. Medication Guide.

The new safety information added to the label including: neuropsychiatric events, hypersensitivity/angioedema, and serious skin reactions should be presented in a patient friendly language under **"What is the most important information I should know about CHANTIX?"**.

Because Chantix is not an antidepressant, as opposed to drugs with antidepressive properties given for smoking cessation, the Medication Guide should convey the message that Chantix should be stopped if a patient develops neuropsychiatric symptoms including depression. To help recognize the potential neuropsychiatric side effects that require medical attention, a decision was made that to include a detailed list of symptoms that patients and caregivers should look for under **"What is the most important information I should know about CHANTIX?"**. The list of symptoms is proposed by the Division and is based on the class labeling for antidepressants. It was adjusted by adding or removing some terms to reflect the range of symptoms that had been observed in patients taking Chantix. For example, the terms irritability and insomnia were deleted, because these are expected symptoms and not reasons to stop the medication.

Accidental injuries and their possible relation to events causing impairment of the driving ability reported in patients using Chantix (somnolence, dizziness, loss of consciousness and difficulty concentrating) should be described under "**What should I avoid while taking CHANTIX?"**.

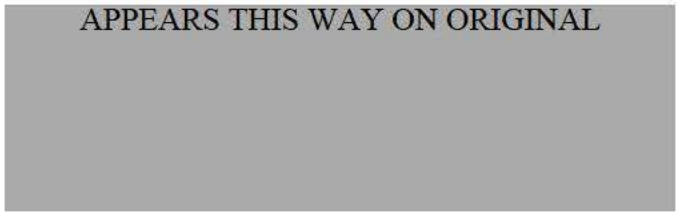
2.6. Dear Health Care Professional Letter.

Detailed review of the DHCP letter was performed by Mathilda Fienkeng (DDMAC) with comments provided in the memorandum dated May 5, 2009.

In summary, the DHCP letter should communicate all of the labeling changes that represent a serious health concern including: suicidality-related events, angioedema, serious skin reactions and accidental injuries. The boxed warning should apply the changes presented in the full product insert. Promotional and efficacy claims should be revised or deleted.

3. Regulatory Action

I recommend approval of the application, pending agreement with the Sponsor on the wording of the revised label.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/s/

Anjelina Pokrovnichka
6/15/2009 02:42:21 PM
MEDICAL OFFICER

Celia Winchell
6/15/2009 03:14:16 PM
MEDICAL OFFICER
Concur

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021928/S-011

OTHER 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

Addendum to the 3-year REMS Assessment Review For Chantix

Date:	May 10, 2013
Reviewer:	Doris Auth, Pharm.D. Assessment Team Leader Division of Risk Management
Associate Director:	Mary Willy, Ph.D. Division of Risk Management
Drug Name(s):	Chantix (varenicline)
Therapeutic Class:	Smoking cessation agent
Dosage and Route:	Oral tablet 0.5mg and 1mg
Application Type/Number:	NDA 21928
Applicant/sponsor:	Pfizer
OSE RCM #:	2012-2458
TSI #:	1134

1 INTRODUCTION

This review serves to summarize discussions between the Division of Risk Management (DRISK) and the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) following the 3-year assessment review for Chantix.

2 BACKGROUND

Chantix is a nicotinic receptor partial agonist approved as an aid to smoking cessation treatment. The Chantix REMS was approved on October 19, 2009. The overall goal of the Chantix REMS is "to (b) (4) the potential risk of serious neuropsychiatric symptoms in patients taking Chantix." As part of the REMS, the FDA requires a Chantix Medication Guide (MG) to be dispensed with every prescription of Chantix and a periodic assessment of the effectiveness of the MG as a tool to inform patients about potential serious risks associated with the use of Chantix, including risks of neuropsychiatric symptoms, (b) (4)

The REMS elements include:

1. Medication Guide
2. Timetable for Submission of Assessments
   18 months, 3- and 7-years after approval

The Assessment Plan for the Chantix REMS includes the following:

An evaluation of patients' understanding of the serious risks of Chantix.

3. MATERIALS REVIEWED

- October 9, 2009 Chantix REMS and REMS Approval letter
- December 20, 2012, DRISK review [J.Ju] of 3-year Chantix REMS Assessment
- February 15, 2013, Patient Labeling review [S. Mills] of Chantix Medication Guide
- February 28, 2013, DRISK REMS memo [D. Smith]

4 DISCUSSION

The 3-year Chantix REMS Assessment was reviewed by DRISK (J. Ju December 20, 2012) and discussions were held with DAAAP regarding the findings. The patient survey results submitted as part of the assessment demonstrated that the knowledge of the serious neuropsychiatric risks of Chantix was adequate, (b) (4) The Patient Labeling Team felt that improvements could be made to the Medication Guide which might lead to a stronger understanding of all of the risks of Chantix, and a REMS Modification Notification letter was planned in which the sponsor would be notified to revise the Medication Guide. Prior to clearance of this letter, it was determined that additional discussion between DRISK and DAAAP was necessary to explore other options for modification of the REMS. The group decided that since the Chantix REMS was approved to solely address the neuropsychiatric risks, a REMS

modification to update the goals of the REMS to more clearly reflect the program's intent should be planned. This modification will also include updates to the Medication Guide.

5 CONCLUSION

DRISK and DAAAP agree that a modification to the Chantix REMS is required to revise the REMS goals to focus only on neuropsychiatric risks. Future assessments of the Chantix REMS should focus only on patient knowledge of the neuropsychiatric risks.

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/s/

DORIS A AUTH
05/10/2013

MARY E WILLY
05/10/2013
I concur

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

Risk Evaluation and Mitigation Strategy (REMS) Memo

Date:	February 28, 2013
Reviewer(s):	Danielle Smith, PharmD, MS DRISK
Team Leader:	Reema Mehta, PharmD, MPH DRISK
Division Director	Claudia Manzo, PharmD, DRISK
Drug Name(s):	Chantix (varenicline)
Therapeutic Class:	Smoking Cessation Agent
Dosage and Route:	Oral tablet 0.5mg and 1mg
Application Type/Number:	NDA 21-928
Applicant/sponsor:	Pfizer
OSE RCM #:	2012-2458
TSI #:	1134

1. INTRODUCTION

On December 7, 2012, the Division of Risk Management (DRISK), Division of Pharmacovigilance, Division of Analgesics, Anesthetics, and Addiction Products (DAAAP), Division of Medical Policy Programs Patient Labeling Team (PLT), and the Office of Compliance met to discuss the findings based on the data in the 3-year Risk Evaluation and Mitigation Strategy (REMS) Assessment report for Chantix (varenicline), NDA 021928, submitted by Pfizer on October 17, 2012. Because of the low awareness of (b) (4), and room to improve in understanding the serious neuropsychiatric adverse events, the team recommended opening the 90 day discussion period to develop strategies to improve patients' knowledge on these key risk messages listed above.

2. BACKGROUND

Chantix (varenicline) is a high-affinity selective partial agonist of the α4β2 nicotinic receptor. The α4β2 nicotinic receptor has been shown to be responsible for the reinforcing properties of nicotine in animal models. Based on the activity at the nicotinic receptor, varenicline could be expected to mitigate withdrawal symptoms and reduce the reinforcing effects of nicotine, leading to efficacy in helping smokers stop smoking. On May 10, 2006, the Agency approved Chantix as an aid to smoking cessation treatment.

On May 16, 2008, the Agency requested the Sponsor submit a proposed REMS due to post-marketing reports of neuropsychiatric symptoms, including changes in behavior, agitation, depressed mood, and suicidal thoughts or actions associated with Chantix.

On October 19, 2009, the Agency approved the REMS for Chantix, which is a Medication Guide-only REMS. The goal of the REMS is "to (b) (4) the potential risk of serious neuropsychiatric symptoms in patients taking Chantix". The timetable for submission of assessments is 18 months, 3- and 7-years after approval

3. REGULATORY HISTORY

On October 17, 2012, Pfizer, Inc. submitted a 3-year REMS assessment report.

On December 7, 2012, the review team met to discuss the findings submitted by Pfizer in the 3-year REMS Assessment report for Chantix. Overall, the findings of this 3-year assessment survey are similar to the previous survey (18-month assessment).[1] The team concluded that patients did not clearly understand the risks and/or serious side effects in the, "What is the most important information I should know about CHANTIX?" section of the Medication Guide and that revisions to the Medication guide were needed.

4. DISCUSSION AND CONCLUSION

The team met to determine if additional risk mitigation measures or revisions to the REMS were warranted. Based on the REMS assessment findings and goal of the REMS

[1] DRISK review of Chantix 18-month Assessment report; Reviewer: J. Ju (dated December 20, 2012).

program, the team recommended revising the Medication Guide to address poor understanding of (b) (4) associated with Chantix by updating the, "What is the most important information I should know about CHANTIX?" section of the Medication Guide, and improving other sections of the Medication Guide to be consistent with the language in the approved labeling. Additional risk mitigation measures for the Chantix REMS program were not identified as necessary at this time by the review team.

The revisions recommended by PLT to the Medication Guide have been agreed upon by the review team and are included in a separate review.[2] The proposed revisions to the Medication Guide will require a REMS modification

5. RECOMMENDATIONS TO DAAAP

DRISK recommends OND, DAAAP send a REMS Modification Notification Letter to the Sponsor for revisions to the Medication Guide. Once the Sponsor submits the REMS Modification, DAAAP should consult DRISK for review of the supplement.

[2] DMPP/Patient Labeling Review of Medication Guide (MG) in response to 3-year Risk Evaluation and Mitigation Strategy (REMS) Assessment Report; Reviewer: Sharon Mills (dated February 15, 2013).

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/s/

DANIELLE SMITH
02/28/2013

CLAUDIA B MANZO
02/28/2013
concur

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

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

Memorandum

Date: February 15, 2013

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

From: L. Shenee Toombs, Regulatory Review Officer, DCDP

CC: Eunice Chung-Davies, Pharm.D., Regulatory Review Officer
Division of Professional Drug Promotion (DPDP)
Olga Salis, Senior Regulatory Health Project Manager (OPDP)
Michael Wade, Regulatory Health Project Manager (OPDP)

Subject: NDA 021928
DCDP labeling comments for CHANTIX ® (varenicline) Tablets
Medication Guide

DCDP has reviewed two proposed Medication Guides (Med Guide) for CHANTIX ® (varenicline) Tablets (Chantix) that were submitted for consult on January 31, 2013. DCDP's comments on the proposed Medication Guides are based on the draft marked versions of the Medication Guides provided in the consult from DAAAP dated January 31, 2013.

We note that the proposed revisions are to ensure information on the risks associated with Chantix are being adequately communicated to patients as determined by DRISK's 3-year REMS assessment.

DCDP has no comments on the proposed changes to the draft Medication Guides at this time.

Thank you for the opportunity to comment on these proposed materials.
If you have any questions, please contact Shenee' Toombs at (301) 796-4174 or latoya.toombs@fda.hhs.gov.

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/s/

LATOYA S TOOMBS
02/15/2013

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

PATIENT LABELING REVIEW

Date:	February 15, 2013
To:	Bob A. Rappaport, M.D. Director **Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	DMPP Review of Medication Guide (MG) in response to 3-year Risk Evaluation and Mitigation Strategy (REMS) Assessment Report
Drug Name (established name):	CHANTIX (varenicline)
Dosage Form and Route:	Tablets, Oral
Application Type/Number:	NDA 21-928
Applicant:	Pfizer, Inc.

1 INTRODUCTION

This review is written in response to a request by the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) for the Division of Medical Policy Programs (DMPP) to review the Applicant's 3-year Risk Evaluation and Mitigation Strategy (REMS) assessment report for CHANTIX (varenicline) Tablets.

On October 17, 2012, Pfizer, Inc. submitted a 3-year REMS assessment report for CHANTIX (varenicline) Tablets. On December 7, 2012, the Division of Risk Management, the Division of Medical Policy Programs, the Division of Pharmacovigilance II (DPV II), the Division of Anesthesia, Analgesia, and Addiction Products, and the Office of Compliance met to discuss the conclusions of the 3-year REMS assessment report for CHANTIX (varenicline) Tablets.

The members of the REMS assessment team reviewed the patient survey findings submitted in the 3-year REMS assessment report and found that patients did not clearly understand the risks and/or serious side effects in the, "What is the most important information I should know about CHANTIX?" section of the Medication Guide (MG). The REMS assessment team agreed that the MG component of the REMS was not meeting its goals and MG revisions were needed.

2 MATERIAL REVIEWED

- 3-year REMS assessment report submitted on October 17, 2012
- Draft DRISK 3-year REMS assessment report dated November 2012.
- CHANTIX (varenicline) Tablets MG approved on December 11, 2012.

3 RECOMMENDATIONS

As a result of the patient survey findings submitted in the 3-year REMS assessment report, the Patient Labeling Team is recommending revisions to the, "What is the most important information I should know about CHANTIX?" section of the MG.

Our review of the MG is appended to this memorandum. The attached marked up and clean MG reflect revisions to the currently approved MG that have been agreed upon by DMPP, DAAAP, DRISK, and DPV II to date, based on the findings of the 3-year REMS assessment report, and efforts to make the MG more concise. The MG revisions will require a REMS modification.

Please let us know if you have any questions.

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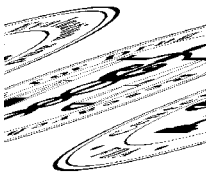
/s/

SHARON R MILLS
02/15/2013

BARBARA A FULLER
02/15/2013

LASHAWN M GRIFFITHS
02/15/2013



Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Compliance

Memorandum

TO: NDA 021928/Supplement 11

THROUGH: Suzanne Barone, Ph.D., Team Leader
Compliance Risk Management and Strategic Problem Solving Team
Division of Compliance Risk Management and Surveillance
Office of Compliance (OC)

FROM: Marcia Britt Williams, Ph.D., Consumer Safety Officer
Compliance Risk Management and Strategic Problem Solving Team
Division of Compliance Risk Management and Surveillance
Office of Compliance

SUBJECT: 18-month Risk Evaluation and Mitigation Strategy (REMS) Assessment Review

DRUG: Chantix (Varenicline) Tablets

NDA 021928/Supplement 11

Background

Varenicline was approved in the United States (as Chantix) in May 2007 as an aid to smoking cessation treatment in adults. Patients attempting to quit smoking with Chantix have reported the occurrence of neuropsychiatric symptoms including depression, changes in behavior, agitation, suicidal ideation, and suicide attempts. In response to these post-marketing reports of nerupsychiatric symptoms, the Chantix Package Insert (PI) was updated in November 2007 and January 2008. The PI was updated in May 2008 to state that patients experiencing certain neuropsychiatric symptoms should stop taking Chantix and contact their physician right away. The Chantix Medication Guide for patients was approved by the FDA at that time as part of risk evaluation and mitigation strategy.

The approved Chantix (Varenicline) Tablets REMS elements include a Medication Guide and timetable for submission of assessments.

Pfizer, Inc., the sponsor for Chantix (Varenicline) Tablets, committed to conduct assessments of the effectiveness of the REMS programs at 18 months, 3 years and 7 years after FDA approval of the initial Chantix (Varenicline) Tablets REMS on October 19, 2009.

The requirements for assessments of an approved REMS under section 505-1(g)(3) include, in section 505-1(g)(3)(B) and (C), requirements for information on the status of any post-approval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue.

OC Observations

1. The Chantix (Varenicline) Tablets 18-month REMS assessment was received by FDA on April 13, 2011. The due date for submission of the assessment was April 19, 2011. The submission was received on time.

2. The approval letter for the Chantix (Varenicline) Tablets REMS requested Pfizer report patients' understanding of the risks of Chantix in their assessment reports.

   OC observation
   Pfizer, Inc. contracted with [redacted] (b) (4) to survey patients' understanding of the serious risks of Chantix (Varenicline) Tablets identified in the Medication Guide. The survey results indicated that 93 percent of respondents remembered receiving a Medication Guide. OC defers analysis of the data to OSE and OND.

3. The timetable for submission is acceptable as provided in the approved REMS.

4. The sponsor did not provide a status update of any post-approval study(ies) or clinical trials in their 18-month assessment report. OC defers to OND and OSE for further details.

OC recommendations to Pfizer via OND:

1. Provide the complete date of the initial approval (inclusive of the month, day and year) at the top of the first page of future REMS modifications and assessments associated with the Chantix (Varenicline) Tablets REMS.
2. Provide an update on any post-approval studies or clinical trials currently underway for Chantix.

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/s/

MARCIA B WILLIAMS
06/21/2011

SUZANNE BARONE
06/24/2011

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

Date:	June 15, 2011
To:	Bob A. Rappaport, MD, Director Division of Analgesic Anesthetic, and Addiction Products (DAAAP)
Through:	Mary Willy, Ph.D., Deputy Director Division of Risk Management (DRISK) Robert Shibuya, MD., Team Leader Division of Risk Management (DRISK)
From:	Jeanne Perla, Ph.D. Social Science Reviewer Division of Risk Management
Subject:	DRISK Review of 18-Month REMS Assessment Report
Drug Name(s):	Chantix Tablets (varenicline tartrate)
Date of Submission:	April 13, 2011
Application Number:	NDA 21-928
Applicant:	Pfizer
OSE RCM #:	2011-1246

1 INTRODUCTION

This memorandum provides a review and comments from the Division of Risk Management (DRISK) in response to the Risk Evaluation and Mitigation Strategy (REMS) 18-month assessment report for Chantix (varenicline tartrate).

2 MATERIAL REVIEWED

- October 19, 2009, Chantix REMS and REMS approval letter
- April 22, 2010, Modified REMS and REMS approval letter
- September 24, 2010, DRISK review [J Stansbury] of proposed methodology to assess Chantix REMS
- April 13, 2011, Chantix 18-month REMS Assessment Report

3 BACKGROUND

Chantix is a nicotinic receptor partial agonist approved as an aid to smoking cessation treatment. The Chantix REMS was approved on October 19, 2009. On April 22, 2010 the REMS was modified to include a new section in the Medication Guide "Who should not take Chantix." The REMS was required to mitigate the risk associated with Chantix, specifically: the potential risk of serious neuropsychiatric symptoms in patients taking Chantix.

The goal is to inform patients about the serious risks associated with the use of Chantix including the potential risk of serious neuropsychiatric symptoms in patients taking Chantix

The REMS Elements include:

1. Medication Guide
2. Timetable for Submission of Assessments
    - 18-months, 3- and 7-years after FDA approval

The REMS includes a requirement that the applicant assess the effectiveness of the REMS in reaching the goal. The Medication Guide is included in Chantix's unit-of-use packaging, therefore, an assessment of the distribution and receipt of the Medication Guide is not required.

The Assessment Plan for the Chantix REMS includes the following:

- An evaluation of patients' understanding of the serious risks of Chantix.

The applicant submitted the 18-month assessment on April 13, 2011. The submission contained results from the patient survey. The objective of the survey was to assess the effectiveness of the REMS in meeting the goal to inform patients about the serious risks associated with the use of Chantix including the potential risk of serious neuropsychiatric

symptoms in patients taking Chantix. The survey also assessed the distribution of the Medication Guide to patients.

4 RESULTS

4.1. Patient Survey

A total of 3,568 eligible (≥ 18 years old, dispensed Chantix between 2/1/09 and 7/31/10, minimum 6 months continuous enrollment in health plan, not in a previous survey) were sent a survey invitation in the mail. Of those, 640 (18%) responded and 633 answered at least one risk comprehension question which met the study definition of completing the survey. There was no imputation of missing values. Data was used from every questionnaire for the survey responders for the questions that were answered. If any question was not answered, the response was coded as having no answer for the respective question.

The demographic information provided indicates that 89% of the respondents were between the ages of 30-64, 51% were males, 59% were Caucasian and 74% had at least graduated from high school. Inclusion criteria consisted of having a least one dispensing of Chantix between February 1, 2009 and July 31, 2010, being 18 years of age of older, having both medical and pharmacy benefits, and did not participate in a previous (b) (4) or Chantix survey in the past 12 months. To thank respondents for their time and consideration, respondents would receive a $30.

The Chantix Medication Guide contains three primary risks in the "Most Important Information" section. The risks are:

1. The potential risk of serious neuropsychiatric symptoms in patients taking Chantix
2. The risk of allergic reactions
3. The risk serious skin reactions

In discussing the primary risks with the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP), we learned that the primary risk to be conveyed to patients is the potential for psychiatric adverse events.

The applicant tested for awareness of all three risks by asking 1) Which symptoms can occur when taking Chantix and 2) Which symptoms would result in the patient stopping drug and seeking medical attention. The third question tangentially asked about the neuropsychiatric risk by asking what medical conditions are important to tell your doctor prior to taking Chantix.

629 patients responded to the following question.

- Which of the following symptoms may be associated with taking Chantix, either during or shortly after the course of treatment? (choose all that apply)
    - 81% responded correctly "Changes in behavior, agitation, depressed mood, suicidal thoughts or actions" (Risk 1)

- 24% responded correctly "Serious allergic reactions" (Risk 2)
- 19% responded correctly "Serious skin reactions" (Risk 3)
- 10% responded incorrectly "Cough, wheezing or chest tightness"
- 18% responded incorrectly "Loss of appetite"
- 6% responded incorrectly "Bone pain"
- 3% responded incorrectly "Hair loss"
- 1% responded incorrectly "Blood infections"
- 10% responded "None of the above"
- 5% responded "I don't know"

628 patients responded to the following question.

- Some of the symptoms below may be associated with taking Chantix. Which of them would require you to stop taking Chantix and seek medical attention immediately? (choose all that apply)
    - 82% responded correctly "Changes in behavior, agitation, depressed mood, suicidal thoughts or actions" (Risk 1)
    - 51% responded correctly "Serious allergic reactions" (Risk 2)
    - 38% responded correctly "Serious skin reactions" (Risk 3)
    - 24% responded incorrectly "Cough, wheezing or chest tightness"
    - 20% responded incorrectly "Blood infections"
    - 16% responded incorrectly "Bone pain"
    - 13% responded incorrectly "Hair loss"
    - 11% responded incorrectly "Loss of appetite"
    - 5% responded "None of the above"
    - 6% responded "I don't know"

630 patients responded to the following question.

- Which of the following medical condition (s) should you tell your doctor you have/had before you start to take Chantix? (choose all that apply)
    - 71% responded correctly "Depression or other mental health "problems (Risk 1)
    - 29% responded "Diabetes"
    - 33% responded "Heart problems"
    - 32% responded "Kidney problems"
    - 31% responded "Liver problems"
    - 24% responded "Asthma"
    - 10% responded "None of the above"
    - 9% responded "I don't know"

The applicant states that 62% of respondents chose the correct response to all 3 neuropsychiatric symptoms; 81% chose 2 or more of the 3 correct responses; 91% chose at least one of the three correct responses; and 8% had no correct response. The applicant suggests that approximately 71% of respondents correctly identified the potential risks of neuropsychiatric symptoms with Chantix.

The sponsor conducted several subanalyses. One compared the results of the survey by whether or not patients reported having read the Medication Guide (Table 1) and one

compared the results by the length of time between dispensing of Chantix (presumed reading of Medication Guide) and the start of survey (Table 2).

Table 1: Survey results by reported Medication Guide reading status

Question	Read Medication Guide		Did Not Read Medication Guide	
	n=547	%	n=86	%
Which of the following medical condition (s) should you tell your doctor you have/had before you start to take Chantix? (choose all that apply)				
o Diabetes	163	30	18	21
o Heart problems	192	35	20	23
o Liver problems	172	31	24	28
o Kidney problems	181	33	22	26
o Depression or other mental health problems*	**406**	**74**	**45**	**52**
o Asthma	138	25	17	20
o None of the above	54	10	9	10
o I don't know	34	6	24	28
Which of the following symptoms may be associated with taking Chantix, either during or shortly after the course of treatment? (choose all that apply)				
o Bone pain	34	6	3	3
o Changes in behavior, agitation, depressed mood, suicidal thoughts or actions*	**450**	**82**	**65**	**76**
o Cough, wheezing or chest tightness	54	10	7	8
o Serious allergic reactions*	**135**	**25**	**20**	**23**
o Blood infections	8	1	1	1
o Serious skin reactions*	**109**	**20**	**10**	**12**
o Loss of appetite	105	19	12	14
o Hair loss	17	3	1	1
o None of the above	58	11	5	6
o I don't know	18	3	15	17
Some of the symptoms below may be associated with taking Chantix. Which of them would require you to stop taking Chantix and seek medical attention immediately? (choose all that apply)				
o Bone pain	89	16	15	17
o Changes in behavior, agitation, depressed mood, suicidal thoughts or actions*	**455**	**83**	**63**	**73**
o Cough, wheezing or chest tightness	136	25	18	21

o Serious allergic reactions*	**283**	**52**	**40**	**47**
o Blood infections	107	20	17	20
o Serious skin reactions*	**216**	**39**	**27**	**31**
o Loss of appetite	62	11	7	8
o Hair loss	71	13	12	14
o None of the above	29	5	3	3
o I don't know	25	5	15	17

* Correct response related to Risk Message

Table 2: Survey results by time between Chantix dispensing and start of survey (selected results)

Awareness of	**"Lag" of 92-183 days (N=228)**		**"Lag" of 184-365 days (N=251)**		**"Lag" of >365 days (N=154)**	
	n	%	n	%	n	%
Knew that neuropsychiatric symptoms could occur	185	81	200	80	130	84
Knew that allergic reactions could occur	60	26	68	27	27	18
Knew that skin reactions could occur	55	24	45	18	19	12
Knew to stop drug & seek help for neuropsychiatric reactions	185	81	204	81	129	84
Knew to stop drug & seek help for allergic reactions	121	53	124	49	78	51
Knew to stop drug & seek help for skin reactions	93	41	89	35	61	40
Knew to tell doctor about history of depression or other psychiatric disorder	163	72	181	72	107	69

4.2 Distribution and dispensing of the Medication Guide

Chantix is packaged in unit-of-use; therefore an assessment on distribution and dispensing of the Medication Guide is not necessary. However, the patient survey included questions to assess the distribution of the Medication Guide:

- 93% (n=587) of patients reported obtaining the Chantix Medication Guide
    - Within the Chantix package: 85%
    - From the doctor's office: 16%
    - From the pharmacy: 15%
- 91% (n=535) of those who reported obtaining the Medication Guide reported they read all or part of the Medication Guide
- Among all respondents:
    - 33% indicated someone in the doctor's office had offered to explain the Medication Guide

- 28% indicated someone in the pharmacy had offered to explain the Medication Guide
- 4% indicated a family member or friend had offered to explain the Medication Guide
- 42% indicated no one had offered to explain the Medication Guide

4.3 Applicant's overall assessment of whether the REMS is meeting the goals

The applicant did not make any assertion regarding whether or not the REMS is meeting the goals.

5 STATUS OF POST APPROVAL STUDIES AND CLINICAL TRIALS

The REMS assessment report for Chantix included an update of the postapproval clinical trial undertaken to investigate safety issues. Difficulties impacting completion of Study A3051123, entitled, "A Phase 4, Randomized, Double-Blind, Active- and Placebo-Controlled, Multicenter Study Evaluating the Neuropsychiatric Safety and Efficacy of 12 Weeks of Varenicline Tartrate 1 mg BID for Smoking Cessation in Subjects with and without a History of Psychiatric Disorders," were described in an email dated June 2, 2011. FDA will follow up on the status of this trial separately.

6 DISCUSSION

The aim of a DRISK REMS assessment review is to determine (1) whether the report is complete, and (2) whether the REMS is meeting the goal.

This assessment report is technically complete and addresses all issues outlined in the approved REMS assessment plan.

The goal is to inform patients about the serious risks associated with the use of Chantix, particularly the potential risk of serious neuropsychiatric symptoms in patients taking Chantix. Our review of the patient knowledge survey focuses on questions related to risk-specific information contained in "What is the most important information I should know about Chantix?" section of the Medication Guide.

The patient survey results showed a high awareness of the potential for serious neuropsychiatric adverse reactions with Chantix, the importance of informing the prescriber of a history of psychiatric illness, and to stop taking Chantix and to seek medical attention if psychiatric symptoms arise. We note that less than 25% of the respondents are aware that symptoms of allergic reactions and serious skin reactions may be associated with taking Chantix, and only 51% of respondents are aware that serious allergic reactions and 38% are aware that serious skin reactions would require them to stop taking Chantix and seek medical attention immediately. However, we understand that serious neuropsychiatric adverse reactions are the primary risks for patients to understand.

The subanalyses showed that patients who reported having read the Medication Guide had a consistently higher rate of answering the questions correctly although the difference was small in magnitude. The significance of this finding is not entirely clear because it might be confounded by differences in people who would or would not read such information.

It was interesting to note that awareness of the key risk messages did not seem to vary with the time interval between when the Medication Guide was presumed to have been read and when the survey was administered.

Because patients had high awareness of the psychiatric risks of Chantix, we consider that the REMS is meeting its goal.

7 RECOMMENDATIONS

On June 2, 2011 DRISK, Division of Pharmacovigilance, DAAAP, and the Office of Compliance met to discuss this conclusion based on the data in the assessment report.

The Medication Guide was recently revised, May 19, 2011 in response to supplement S-021. As noted before, because patients showed high awareness of the key risk message (neuropsychiatric events), we do not recommend changes to this REMS. We recommend the applicant be sent a REMS assessment complete letter.

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/s/

JEANNE P PERLA
06/15/2011

ROBERT B SHIBUYA
06/16/2011

MARY E WILLY
06/16/2011
I concur

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

Date:	September 24, 2010
To:	Bob Rappaport, M.D., Director **Division of Anesthesia and Analgesia Products (DAAP)**
Through:	Jodi Duckhorn, M.A., Team Leader **Division of Risk Management (DRISK)**
From:	James P. Stansbury, Ph.D., M.P.H., Social Science Reviewer **Division of Risk Management (DRISK)**
Subject:	DRISK Social Science Review of Proposed Methodology and Survey Instruments for the Risk Evaluation and Mitigation Strategy (REMS)
Drug Name(s):	Chantix (varenicline tartrate)
Application Type/Number:	NDA 21-928
Applicant/sponsor:	(b) (4)
OSE RCM #:	2010-1811

1 INTRODUCTION

1.1 PURPOSE

This memorandum is in response to a request by the Division of Anesthesia and Analgesia Products (DAAP) for the Division of Risk Management (DRISK) to review the proposed methodology and survey instrument that will be used to assess the effectiveness of the Risk Evaluation and Mitigation Strategy (REMS) for Chantix (varenicline tartrate). Please send these comments to the sponsor within two weeks, and copy DRISK on the correspondence. Let us know if you would like a meeting to discuss these comments before sending them to the sponsor.

1.2 BACKGROUND

Chantix (varenicline tartrate) is a nicotinic acetylcholine receptor partial agonist indicated for use in smoking cessation. The REMS was initially approved October 19, 2009, and modified on April 4, 2010. The REMS includes a Medication Guide and timetable for assessment.

The sponsor's most recent submission, received August 5, 2010, included the methodology and instrument proposed to assess the goal of the REMS. The revised methodology and instrument responded to DRISK's review, dated February 7, 2010. The sponsor's submission also included a report detailing a pilot study using the earlier version of the REMS assessment questionnaire.

2 MATERIALS REVIEWED

- Chantix (varenicline tartrate) Risk Evaluation and Mitigation Strategy (REMS), approved October 19, 2009, and modified April 22, 2010
- Chantix (varenicline tartrate) Risk Evaluation and Mitigation Strategy (REMS) approval letters, dated October 19, 2009 and April 22, 2009
- DRISK Review of Patient Labeling (Medication Guide), Proposed Risk Evaluation and Mitigation Strategy Modification (REMS), and Proposed Methodology and Survey Instruments for REMS Assessments, dated February 7, 2010.
- Chantix (varenicline tartrate) Risk Evaluation and Mitigation Strategy (REMS) proposed assessment protocol (methodology and survey instruments), and pilot study results, submitted August 5, 2010 for assessment due April 18, 2011.

3 CONCLUSIONS AND RECOMMENDATIONS

We have the following comments and recommendations for Pfizer:

Methods

1. To reduce the potential for selection bias and low response rate shown by the pilot study, randomly sample participants from the proposed frame (that is, eligible Chantix users in the NHI database). To achieve the target sample size and avoid

volunteer bias, sample across a time interval (that is, range of months during which individuals were dispensed Chantix).

2. Add an additional mechanism to remind non-respondents about survey participation. An extra targeted reminder using a different medium (telephone, for example) will likely enhance response rate and may reduce the volume of mail proposed.
3. Sample with substitution if your proposed sample size has not been attained following the determination of participants' non-response after seven weeks or direct refusal to participate.
4. Make the following changes to your invitation letter:

   (b) (4) (b) (4) seeks your participation in a brief survey about (b) (4) the risks and safe use of Chantix (varenicline), a smoking cessation medication. This study will provide valuable information about patients' (b) (4) - knowledge about serious risks associated with Chantix (b) (4)

   The study is being conducted by i3…and is sponsored by Pfizer, the manufacturer of (b) (4) . The study is required by the U.S. Food and Drug Administration (FDA)… You were randomly chosen *[If this is an accurate statement it need not be changed—if the frame is sorted to select those most recently dispensed Chantix as proposed, the word random should be deleted and the sentence end: "…were recently dispensed Chantix."]*

   …

   …To thank you for your time and consideration, i3 will provide a $30.00 incentive if you respond to the survey through one of the two methods. [*Sponsor, upon its discretion, may add a clause that only completed questionnaires or interviews will receive the respondent gift if this is the determined policy.*]

   …

5. Revise your proposed reminder letter addressing the same points:
   - (b) (4) seeks the addressee's participation in a survey, but not a research study.
   - The objective is an assessment of patient knowledge about risk and safe use.
   - FDA requires this assessment be conducted by the makers of Chantix.
   - Refer to random selection only if true, otherwise refer to recent dispensing.

Reporting

6. Report results from key risk questions prominently. Lead with results from proposed Tables 6 and 7 in your discussion and conclusions, and assure key findings about risk knowledge are reported in the executive summary. These indicators serve as best evidence for evaluating the REMS.

7. Include a specific statement about whether the REMS is meeting its goals and whether modifications are needed.

Please let us know if you have any questions.

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/s/

JAMES P STANSBURY
09/24/2010

JODI M DUCKHORN
09/24/2010

REGULATORY PROJECT MANAGER LABELING REVIEW

Division of Anesthesia, Analgesia, and Rheumatology Products

Application Number: NDA 21-928/SLR-011

Name of Drug: Chantix (varenicline) tablets, 0.5 mg and 1 mg

Applicant: Pfizer, Inc.

Material Reviewed:

Submission Date(s): SLR-011: September 5, 2008, April 30, and July 15, 2009

Receipt Date(s): SLR-011: September 5, 2008, May 1, and July 15, 2009

Submission Date of Structure Product Labeling (SPL): N/A

Type of Labeling Reviewed: REMS proposal

Reviews Completed: Ayanna Augustus, Ph.D., Regulatory Project Manager, October 13, 2009
Parinda Jani, Chief, Project Management Staff, -concur
Celia Winchell, M.D., Clinical Team Leader, -concur
Jodi Duckhorn, MA, Team Leader, DRISK/OSE May 12, 2009

Background and Summary

Pfizer, Inc., was notified in a letter dated May 16, 2008, that a Risk Evaluation and Mitigation Strategy (REMS) was necessary for Chantix in order to address the new safety information on the risks of neuropsychiatric symptoms, including changes in behavior, agitation, depressed mood, and suicidal thoughts or actions. Additional recommended revisions were communicated to the sponsor in a letter dated, April 1, 2009. DRISK/OSE completed a review of the REMS proposal and recommended several changes to the REMS supporting document and the proposed evaluation methodology. These comments were conveyed to the Sponsor in an e-mail dated July 10, 2009. The sponsor agreed to the revisions and submitted a revised REMS on July 15, 2009.

Review

See DRISK/OSE review dated May 12, 2009. The revised REMS proposal submitted by the sponsor on July 15, 2009, contains the recommended revisions outlined the May 12, 2009, review.

Recommendations

There were no changes made to the package insert or the Medication Guide. The revised proposed REMS submitted on July 15, 2009, is recommended for approval.

Ayanna Augustus, Ph.D.
Regulatory Project Manager

Supervisory Comment/Concurrence:

Parinda Jani
Chief, Project Management Staff

Celia Winchell, M.D.
Clinical Team Leader

Drafted: AA/8/13/09
Revised/Initialed:
Finalized:
Filename: CSO Labeling Review Template (updated 1-16-07).doc

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21928	SUPPL-11	PFIZER INC	CHANTIX

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/s/

AYANNA S AUGUSTUS
10/15/2009

PARINDA JANI
10/15/2009

CELIA J WINCHELL
10/15/2009
Concur

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

Date:	May 12, 2009
To:	Bob Rappaport, M.D., Director
	Division of Analgesics, Anesthetics and Rheumatology Products
Through:	Claudia Karwoski, PharmD., Director (Acting)
	Division of Risk Management
From:	Jodi Duckhorn, MA, Team Leader
	Division of Risk Management
Subject:	DRISK Review of Risk Evaluation and Mitigation Strategy
Drug Name(s):	Chantix (varenicline)
Application Type/Number:	NDA 21-928
Applicant/sponsor:	Pfizer
OSE RCM #:	2009-703

1 INTRODUCTION

This review is written in response to a request from the Division of Analgesics, Anesthetics and Rheumatology Products (DAARP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Risk Evaluation and Mitigation Strategy (REMS), which includes the draft Medication Guide (MG) and Timetable for Submission of Assessments of the effectiveness of the REMS.

2 MATERIAL REVIEWED

- Proposed Chantix (varenicline) Risk Evaluation and Mitigation Strategy (REMS), submitted on April 30, 2009.
- Proposed Chantix (varenicline) Risk Evaluation and Mitigation Strategy (REMS), submitted on April 30, 2009.
- Chantix FDAAA REMS Information Request Letter, signed April 1, 2009.
- DRISK Interim Comments on Chantix REMS, provided to DAARP on February 27, 2009.
- Chantix FDAAA Safety Labeling Changes Supplement Request Letter, signed February 19, 2009.
- Proposed Chantix (varenicline) Risk Evaluation and Mitigation Strategy (REMS), submitted on September 5, 2008.
- Chantix FDAAA REMS Notification Request Letter, signed May 16, 2008.

3 BACKGROUND

Since Chantix (varenicline) was approved on May 10, 2006 as an aid to smoking cessation treatment, the FDA has become aware of postmarketing reports of neuropsychiatric symptoms, including changes in behavior, agitation, depressed mood, and suicidal thoughts or actions associated with Chantix (varenicline).

Pfizer originally submitted a proposed REMS for Chantix on September 5, 2008 in response to a REMS request letter May 16, 2008. That letter specified that the REMS should include a Medication Guide, a Communication Plan, and a Timetable for Submission of Assessments. That letter also notified the sponsor that the Medication Guide submitted in supplement S-008 was approved.[1] During the course of our review we noted the Communication Plan submitted by the sponsor contained materials that have been previously disseminated to the medical community. DRISK concluded since the Communication Plan only included materials that were already disseminated and there was no plan at this time to send additional communication to healthcare providers, the elements of the REMS could be limited to a Medication Guide and a Timetable for Submission of Assessments. A letter reflecting this comment as well as other comments

[1] DRISK completed the review of the Chantix (varenicline) Medication Guide on January 31, 2008, and provided verbal recommendations to the Medication Guide in a meeting with DAARP on May 5, 2009.

on the proposed REMS was sent to the company on April 1, 2009. The current REMS submission addresses the comments that were sent in that letter.

Another letter was sent to Pfizer on February 19, 2009 requesting Safety Labeling Changes, including the addition of a boxed warning to highlight the risks above. These labeling changes include revisions to the Medication Guide. Any comments on the Medication Guide will be sent in a separate memorandum.

4 DISCUSSION OF PROPOSED REMS

a. Goal

The Applicant has proposed the following REMS goal:

> *To mitigate the potential risk of serious neuropsychiatric symptoms in patients taking Chantix by training patients about appropriate monitoring for psychiatric symptoms unusual to the individual, such as agitation, depressed mood and changes in behavior or if the patient develops suicidal ideation and suicidal behavior.*

b. REMS elements

- Medication Guide: The proposed REMS states that all lots of Chantix currently contain the May 2008 Package Insert and Medication Guide. Chantix prescriptions are dispensed as: Starting Month Pack ((b) (4)% of all prescriptions dispensed), Continuing Month Pack (b) (4), 1 mg bottle of 56 tablets (b) (4), and 0.5 mg bottles of 56 tablets (b) (4). Medication Guide tear pads are also available to hospital pharmacies.
- The Timetable for Submission of Assessments is as follows:
  - 1st assessment: 18 months after approval
  - 2nd assessment: 3 years after approval
  - 3rd assessment: 7 years after approval
- Evaluation: The Applicant proposes to conduct surveys of patients' understanding of both the risks and safe use of Chantix. As part of this survey, the applicant proposes to estimate the proportion of patients who received and read the Chantix Medication Guide. The proposed evaluation will randomly sample from among a claims database used by (b) (4) insurance plan members with both medical and pharmacy benefits.

  The survey will be mailed to 1,925 randomly selected patients who take Chantix, with a goal of receiving 385 responses. Surveys will be mailed to people within three months of filling their Chantix prescription.

  The questionnaire will be pilot tested and findings will be incorporated into the final instrument. The final survey instrument will be submitted to FDA at least 60 days before initiating the assessment.

5 CONCLUSIONS AND RECOMMENDATIONS

DRISK believes that the Applicant's proposed REMS for Chantix (varenicline) generally meets the statutory requirements outlined in 21 CFR 208 and in accordance with 505-1. We have the following comments and recommendations on the proposed REMS Assessment Plan:

1. Some of the content submitted in the April 30, 2009 submission is more appropriate for a REMS Supporting Document. The content of the REMS should be revised.

   - The information in the proposed REMS under the section, "Information Needed for Assessments" is more appropriate for the REMS supporting document.
   - See the appended Chantix (varenicline) REMS proposal (Appendix A) for track changes corresponding to comments in this review.

2. We remind the Applicant of their requirement to comply with 21 CFR 208.24

   - A required statement alerting the dispenser to provide the Medication Guide with the product must be on the carton and container of all strengths and formulations. We recommend the following language dependent upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):

     "Dispense the enclosed Medication Guide to each patient." or

     "Dispense the accompanying Medication Guide to each patient."

   - Sufficient numbers of Medication Guides should be provided with the product such that a dispenser can provide one Medication Guide with each new or refilled prescription. We recommend that each packaging configuration contain enough Medication Guides so that one is provided for each "usual" or average dose. For example:
   - A minimum of four Medication Guides would be provided with a bottle of 100 for a product where the usual or average dose is 1 capsule/tablet daily, thus a monthly supply is 30 tablets.
   - A minimum of one Medication Guide would be provided with unit of use where it is expected that all tablets/capsules would be supplied to the patient.

4. The Applicant's proposed timetable for assessments (18 months, 3 years, and 7 years) is acceptable.

5. The proposed methodology to evaluate the effectiveness of the REMS is generally acceptable. We have the following recommendations to the Applicant with regard to the proposed evaluation:

   - The applicant should add "select all that apply" to questions 4 and 5.
   - Question 6 should be reworded to:

     Assuming that you have these conditions or symptoms, which of them should you tell your doctor before you start to take Chantix (select all that apply):
     a. diabetes
     b. heart problems
     c. depression
     d. liver problems
     e. kidney problems
     f. feel agitated
     g. overweight

h. eating disorder (such as anorexia or bulimia)
i. asthma
j. mental health problems
k. none of the above
l. I don't know

- The Applicant should submit to FDA at least 60 days prior to initiating:
  - the final survey instrument, including the introductory letter that participants will receive
  - all methodology

6. The REMS approval letter should include the following standard language to assess the effectiveness of the MG:

   a. An evaluation of patients' understanding of the serious risks of Chantix (varenicline)

   b. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24

   c. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

   The applicant's submission states that the assessments described in "b" and "c" above are unnecessary because the products are distributed in unit-of-use packaging that contains the Medication Guide. We agree that since the Medication Guide is packaged with the product, the applicant does not need to address distribution and dispensing of the Medication Guide in their REMS assessment.

Please let us know if you have any questions.

Appendix A

NDA 21-928 Chantix (Varenicline)

PROPOSED RISK EVALUATION AND MITIGATION STRATEGIES (REMS)

I. GOAL

To mitigate the potential (b) (4) risk of serious neuropsychiatric symptoms in patients taking Chantix by training patients about appropriate monitoring for psychiatric symptoms unusual to the individual, such as agitation, depressed mood and changes in behavior or if the patient develops suicidal ideation and suicidal behavior.

II. REMS ELEMENTS

A. MEDICATION GUIDE

Pfizer will provide Medication Guides (b) (4) to pharmacists to be given to patients each time Chantix is dispensed to increase patient knowledge of how to safely and effectively use Chantix. Pfizer must provide copies of the Medication Guide for each unit of use bottle. Pfizer will make tear pads containing the Medication Guide (b) (4) available in pharmacies for direct distribution to patients.

(b) (4)

III. ASSESSMENT OF REMS

A. TIMETABLE FOR ASSESSMENTS

REMS Assessments will be submitted to FDA (b) (4) 18 months, 3 years, and 7 years following REMS approval. (b) (4)

(b) (4)

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/s/

Jodi Duckhorn
5/13/2009 04:47:04 PM
DRUG SAFETY OFFICE REVIEWER

Claudia Karwoski
5/14/2009 07:54:32 AM
DRUG SAFETY OFFICE REVIEWER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 021928/S-011

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021928

PRIOR APPROVAL SUPPLEMENT REQUEST
REMS MODIFICATION NOTIFICATION

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 New Drug Application (NDA) for Chantix (varenicline) Tablets; 0.5 mg and 1 mg.

We recently reviewed the Medication Guide while reviewing your October 17, 2012, submission containing the 18-month risk evaluation and mitigation strategy (REMS) assessment for Chantix (varenicline), and have determined that the Medication Guide should be revised in order to facilitate the goals of communicating the risks of Chantix to patients.

To facilitate the goal of informing patients about neuropsychiatric events with Chantix, we request that you revise the "What is the most important information I should know about CHANTIX" section of the Medication Guide as well as other sections of the Medication Guide so as to furnish adequate information for the safe and effective use of the drug (see recommended changes in attached Medication Guide).

Submit draft labeling as a prior approval supplement to this application, incorporating all revisions since the last approval of the package insert. 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 also include annotations that support all proposed changes, including annual reportable changes. Your supplement must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Because the Medication Guide is also part of your approved REMS for Chantix (varenicline), and in accordance with section 505-1(g)(4)(B) of the FDCA, we have determined that your approved REMS for Chantix (varenicline) must be modified to ensure that the benefits of the drug outweigh its risks.

The proposed changes to the Medication Guide and the proposed REMS modification should be submitted in the same supplement within 60 days of the date of this letter.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

NEW SUPPLEMENT FOR NDA 021928
PRIOR APPROVAL LABELING/PROPOSED REMS MODIFICATION

Prominently identify subsequent submissions related to the proposed REMS modification with the following wording in bold capital letters at the top of the first page of the submission:

NDA021928
PRIOR APPROVAL LABELING/PROPOSED REMS MODIFICATION-AMENDMENT

If you do not submit electronically, please send 5 copies of your submission.

If you have any questions, call Katherine Won, Pharm.D., Safety Regulatory Project Manager, at (301) 796-7568.

Sincerely,

{See appended electronic signature page}

Judith A. Racoosin, M.D., M.P.H.
Deputy Director for Safety
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

JUDITH A RACOOSIN
09/04/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021928

REMS ASSESSMENT ACKNOWLEDGEMENT

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 New Drug Application (NDA), 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 your October 17, 2012, submission containing your assessment of the Chantix (varenicline) Tablets risk evaluation and mitigation strategy (REMS).

On December 14, 2012, we notified you by email that we were initiating discussions of your REMS assessment. This letter is a follow-up to that email.

After consultation between the Office of Surveillance and Epidemiology and the Office of New Drugs, we found the REMS assessment to be complete.

If you have any questions, contact Katherine Won, Pharm.D., Safety Regulatory Project Manager, at (301) 796-7568 or katherine.won@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Judith A. Racoosin, M.D., M.P.H.
Deputy Director for Safety
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

JUDITH A RACOOSIN
05/17/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021928

REMS ASSESSMENT ACKNOWLEDGMENT

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

Attention: Lilya I. Donohew, Ph.D.
Director, Worldwide Regulatory Affairs

Dear Dr. Donohew:

Please refer to your New Drug Application (NDA) 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 your April 13, 2011, submission containing your assessment of the Chantix Risk Evaluation and Mitigation Strategy (REMS).

After consultation between the Office of Surveillance and Epidemiology and the Office of New Drugs, we found the REMS assessment to be adequate.

If you have any questions, call Ayanna Augustus, Ph.D., Regulatory Health Project Manager, at (301) 796-3980.

Sincerely,

{See appended electronic signature page}

Rigoberto Roca, M.D.
Deputy Director
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

RIGOBERTO A ROCA
06/23/2011

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANALGESIA, ANESTHESIA, AND RHEUMATOLOGY PRODUCTS
HFD-170, Building 22, 10903 New Hampshire Ave. Silver Spring MD 20993
Tel:(301)796-2280

M E M O R A N D U M

DATE: February 25, 2009

TO: File, NDA 21-928
Chantix (Varenicline) Tablets
Pfizer, Inc
Proposed Risk Evaluation and Mitigation Strategies (REMS)

FROM: Celia Winchell, M.D., Medical Team Leader, Addiction Drug Products,
DAARP, CDER (HFD-170)

THROUGH: Larissa Lapteva, M.D., M.H.S., Deputy Director for Safety, DAARP

RE: Proposed REMS

Background:
Since Chantix was approved on May 10, 2006, as an aid to smoking cessation treatment, postmarketing reports have been received describing neuropsychiatric symptoms, including changes in behavior, agitation, depressed mood, and suicidal thoughts or actions. On May 16, 2008, the Agency sent a REMS Request letter to which Pfizer responded on September 5, 2008. This submission was reviewed by both the Division of Risk Management (DRISK) in the Office of Surveillance and Epidemiology (OSE) and, at DRISK's request, by the Division of Drug Marketing, Advertising, and Communication (DDMAC). Comments have been received from both.

The purpose of this memorandum is to document the rationale for changing the elements of the proposed REMS compared to what elements were required of Pfizer in our May 16, 2008, letter. Secondly, this memorandum captures different divisions' views on the review of the proposed REMS.

OSE and DAARP are in agreement that a communication plan is not needed at this time. The proposed Communication Plan consisted of materials that were already distributed in Pfizer's ongoing efforts to communicate risk information about Chantix. The only new Communication Plan elements described in the REMS were future Dear Healthcare Provider and Dear Pharmacist letters, which Pfizer would distribute in the event of future changes to the Medication Guide or package insert. Although a Communication Plan was required in the original REMS letter dated May 16, 2008, and justified in the original April 29, 2008 REMS memorandum , it appears that in the safety communications issued since the time of this original requirement, Pfizer has adequately communicated the known to date information about the risk of neuropsychiatric symptoms in patients using Chantix. Therefore, we have determined that a Communication Plan to ensure that the benefits of the drug outweigh the risks is not necessary at this time and this element of the REMS may be omitted. An information request letter will be sent to Pfizer noting this. However, should future changes to the Medication Guide or Package Insert require modifications to the approved REMS, it is possible that a Communication Plan may be required in the future if the Secretary determines that such a plan may support implementation of an element of the REMS.

OSE Comments

a. Regarding the stated goal of the REMS in the REMS proposal, OSE has noted that: (b) (4) does not convey a measurable goal and was re-written by DRISK for DAARP review and concurrence."

DRISK proposes the following as an alternative:

Goal – The language should be clear and concise in describing the ultimate REMS goal:
To mitigate the risk of serious neuropsychiatric symptoms in patients taking Chantix by training patients about appropriate monitoring for agitation, depressed mood and changes in behavior or if the patient develops suicidal ideation and suicidal behavior.

DAARP Comment: There are a variety of concerning neuropsychiatric symptoms reported in patients taking Chantix, of which the ones listed above are only examples. Therefore, I recommend that the wording employ language such as "appropriate monitoring for unusual psychiatric symptoms such as…"

b. OSE provided comments and requests for revision on the proposed physicians' survey to be used as part of the evaluation of effectiveness of the Communication Plan.

DAARP Comment: Since the Communication Plan is not required at this time, OSE comments about the physicians' survey should be conveyed to Pfizer as comments for consideration outside the REMS.

c. OSE also recommended that the Medication Guide section of the REMS be revised to read "Pfizer will provide Medication Guides to pharmacists to be given to patients each time Chantix is dispensed to increase the patient's knowledge of how to safely and effectively use Chantix. Pfizer must provide copies of the Medication Guide for each unit of use bottle. Pfizer will make tear pads containing the Medication Guide available in pharmacies for direct distribution to patients."

.*DAARP Comment:* I concur with this recommendation.

2. DAARP Comments

I am in agreement with OSE regarding the Communication Plan and have therefore not reviewed the already-distributed materials characterized as part of the Communication Plan. I have reviewed the proposed patients' and physicians' surveys. Since the communication plan is not necessary at this time, the proposed survey for physicians is not part of the REMS. The [redacted] (b) (4) is part of the current REMS.

In addition to the concerns noted by OSE, with which I concur, I have the following comments and concerns:

Question 6 in the physician survey reads as follows:

> 6) * According to the Chantix PI or label, serious neuropsychiatric symptoms have occurred in patients being treated with Chantix. All patients being treated with Chantix should be observed for which, if any, of the following neuropsychiatric symptoms: (Please select all that apply)
> a. Changes in behavior
> b. Agitation
> c. Depressed mood
> d. Suicidal ideation
> e. Suicidal behavior
> f. Other (Please specify) _____
> g. None of the above
> h. Don't know / Not sure

The wording of this question implies that these specific symptoms are the only ones that have occurred in patients using Chantix. In fact, these are merely examples, and a variety of other neuropsychiatric symptoms have occurred. Patients should be observed for any and all changes in thinking, mood, behavior, perception, or other aspects of neuropsychiatric function. Although this material is not part of the REMS, I recommend that the question should be deleted and replaced with a question which conveys and tests understanding of this concept.

3. DDMAC Comments

DDMAC has objected to a number of statements included in the REMS materials, noting that they are promotional in tone and not appropriate for inclusion in REMS materials. Several of the statements to which DDMAC objects describe the extent of marketing of Chantix, the adverse health effects of smoking, and a lack of clear association between suicide and the use of Chantix from clinical trial data.

DAARP Comment: In general, the Division concurs with DDMAC's advice. As noted above, these materials are actually items that have already been distributed and are not to be considered part of the REMS program. Nevertheless, a number of DDMAC's comments are relevant to future materials that may be developed and distributed by Pfizer in their risk communication efforts and should be provided to Pfizer as advice.

However, the Division believes that some of the statements provide important risk/benefit information that should be conveyed to prescribers. Specifically, these statements (from the list of DDMAC objections to the Dear Health Care Professional and Pharmacist Letters) convey concepts that have also been included in labeling:

1. Please discuss the risks of smoking, the health benefits of quitting smoking, and the product's efficacy and safety profile with your patients. Symptoms experienced in prior quit attempts, with or without CHANTIX, should also be discussed.
2. Cigarette smoking is associated with significant morbidity and mortality… [text omitted]…Patients who smoke cigarettes should be counseled to quit. CHANTIX has been demonstrated to be effective in helping cigarette smokers quit smoking.

These statements, from the list of DDMAC objections to the "What You Need to Know" Tool are factual statements and the promotional nature is not obvious to me:

> 1. In trials, many people who had slip-ups were able to successfully quit at the end of 12 weeks.
>
> 2. No matter how long you've been a smoker, quitting smoking is one of the best things you can do for your health. And taking CHANTIX can help.

Therefore, I do not share DDMAC's concerns about these specific statements and would recommend they be permitted to be included in the materials. I concur with their other comments. The concerns listed above have been discussed with DDMAC and the following agreement was reached:

1. Regarding the language in the future Dear Health Care Provider and Dear Pharmacist letters: To convey the DDMAC's message not to use the promotional statements in the future Dear Health Care Provider and Dear Pharmacist letters, DAARP will send a comment to Pfizer exemplifying the promotional statements

with several such statements identified by the DDMAC and listed in their consult. The two comments indicated above that convey concepts reflected in labeling will not be exemplified as promotional in the comments sent to the Sponsor.

2. Regarding the DDMAC's comments on the promotional tone of the statements in the "What You Need to Know" survey: Given the important public health message that one of the statements recommended by the DDMAC for deletion was to convey, DDMAC agreed to permit retaining in the survey of the following statement:

   No matter how long you've been a smoker, quitting smoking is one of the best things you can do for your health. And taking CHANTIX can help.

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/s/

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