Chantix Label Update
December 2016

Chantix® (varenicline)
Prescribing Information
Information on Chantix, can be accessed via the following link http://labeling.pfizer.com/ShowLabeling.aspx?id=557. In the event this link should not work, please access the product’s Approved Prescribing Information at www.pfizer.com.

This information has been provided for your information, regarding the 2016 Chantix Label Update.

Pfizer does not suggest or recommend the use of varenicline in any manner other than as described in the Prescribing Information.

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Chantix Label Update and Indication

This December 2016 Label update was based upon the results of the EAGLES Study\(^1\) which is referred to as the Postmarketing Neuropsychiatric (NPS) Safety Outcome Trial in the Chantix Prescribing Information\(^2\), simplified to the Neuropsychiatric Safety Study in this presentation.

**Indication:** Chantix is indicated for use as an aid to smoking cessation treatment in adults.

- Smoking cessation therapies are more likely to succeed for patients who are motivated to stop smoking and who are provided additional advice and support. Provide patients with appropriate educational materials and counseling to support the quit attempt.\(^2\)

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2. Chantix USPI, Pfizer Inc., December 2016
# Overview of Changes in U.S. Prescribing Information (USPI)

<table>
<thead>
<tr>
<th>USPI Title (Section)</th>
<th>Topic</th>
<th>Removed</th>
<th>Revised</th>
<th>Added</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boxed Warning</td>
<td>Serious neuropsychiatric (NPS) adverse events</td>
<td>✔️</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warnings and Precautions (Section 5.1)</td>
<td>NPS AE Warning - retained and revised HCP instructions</td>
<td></td>
<td>✔️</td>
<td></td>
</tr>
<tr>
<td>Warnings and Precautions &amp; Clinical Studies (Section 5.1 &amp; 14.9)</td>
<td>FDA expanded NPS analysis of EAGLES safety data</td>
<td></td>
<td>✔️</td>
<td></td>
</tr>
<tr>
<td>Warnings and Precautions (Section 5.1)</td>
<td>Observational NPS safety data and 5- &amp; 18-study NPS safety analyses</td>
<td>✔️</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical Studies (Section 14.9)</td>
<td>EAGLES efficacy results</td>
<td></td>
<td>✔️</td>
<td></td>
</tr>
</tbody>
</table>
WARNING: SERIOUS NEUROPSYCHIATRIC EVENTS

Serious neuropsychiatric events including, but not limited to, depression, suicidal ideation, suicide attempt, and completed suicide have been reported in patients taking CHANTIX. Some reported cases may have been complicated by the symptoms of nicotine withdrawal in patients who stopped smoking. Depressed mood may be a symptom of nicotine withdrawal. Depression, rarely including suicidal ideation, has been reported in smokers undergoing a smoking cessation attempt without medication. However, some of these symptoms have occurred in patients taking CHANTIX who continued to smoke.

All patients being treated with CHANTIX should be observed for neuropsychiatric symptoms including changes in behavior, hostility, agitation, depressed mood, and suicide-related events, including ideation, behavior, and attempted suicide. These symptoms, as well as worsening of pre-existing psychiatric illness and completed suicide, have been reported in some patients attempting to quit smoking while taking CHANTIX in the postmarketing experience. When symptoms were reported, most were during CHANTIX treatment, but some were following discontinuation of CHANTIX therapy.

These events have occurred in patients with and without pre-existing psychiatric disease. Patients with serious psychiatric illness such as schizophrenia, bipolar disorder, and major depressive disorder did not participate in the premarketing studies of CHANTIX.

Advise patients and caregivers that the patient should stop taking CHANTIX and contact a healthcare provider immediately if agitation, hostility, depressed mood, or changes in behavior or thinking that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behavior. In many postmarketing cases, resolution of symptoms after discontinuation of CHANTIX was reported, although in some cases the symptoms persisted; therefore, ongoing monitoring and supportive care should be provided until symptoms resolve.

The risks of CHANTIX should be weighed against the benefits of its use. CHANTIX has been demonstrated to increase the likelihood of abstinence from smoking for as long as one year compared to treatment with placebo. The health benefits of quitting smoking are immediate and substantial. [see Warnings and Precautions (5.1) and Adverse Reactions (6.2)]
Serious neuropsychiatric adverse events have been reported in patients being treated with CHANTIX.

These postmarketing reports have included changes in mood (including depression and mania), psychosis, hallucinations, paranoia, delusions, homicidal ideation, aggression*, hostility, agitation, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed suicide.

Some patients who stopped smoking may have been experiencing symptoms of nicotine withdrawal, including depressed mood.

Depression, rarely including suicidal ideation, has been reported in smokers undergoing a smoking cessation attempt without medication. However, some of these adverse events occurred in patients taking CHANTIX who continued to smoke.

Neuropsychiatric adverse events occurred in patients with and without pre-existing psychiatric disease; some patients experienced worsening of their psychiatric illnesses.

Some neuropsychiatric adverse events, including unusual and sometimes aggressive behavior directed to oneself or others, may have been worsened by concomitant use of alcohol.

* Aggression was not listed in the prior label and was added in this update
Observe patients for the occurrence of neuropsychiatric adverse events.

Advise patients and caregivers that the patient should stop taking CHANTIX and contact a healthcare provider immediately if agitation, depressed mood, changes in behavior or thinking that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behavior.

The healthcare provider should evaluate the severity of the symptoms and the extent to which the patient is benefiting from treatment, and consider options including dose reduction, continued treatment under closer monitoring, or discontinuing treatment.

In many postmarketing cases, resolution of symptoms after discontinuation of CHANTIX was reported. However, the symptoms persisted in some cases; therefore, ongoing monitoring and supportive care should be provided until symptoms resolve.
The neuropsychiatric safety of CHANTIX was evaluated in a randomized, double-blind, active and placebo-controlled trial.

Included subjects without a history of psychiatric disorder (non-psychiatric cohort, N=3912) and subjects with a history of psychiatric disorder (psychiatric cohort, N=4003).

Subjects aged 18-75 years, smoking ≥10 cigarettes per day.

Randomized 1:1:1:1 to CHANTIX 1 mg BID, bupropion SR 150 mg BID, nicotine replacement therapy patch (NRT) 21 mg/day with taper or placebo for a treatment period of 12 weeks.

Followed for another 12 weeks post-treatment.
Neuropsychiatric Safety Study – Composite Endpoint: Clinically Significant NPS Adverse Events

Composite safety endpoint intended to capture clinically significant neuropsychiatric adverse events of:

- Anxiety
- Depression
- Feeling abnormal
- Hostility
- Agitation
- Aggression
- Delusions
- Hallucinations
- Homicidal ideation
- Mania
- Panic
- Paranoia
- Psychosis
- Irritability
- Suicidal ideation
- Suicidal behavior
- Completed suicide
In the non-psychiatric cohort:

- Use of CHANTIX, bupropion and NRT was not associated with an increased risk of clinically significant neuropsychiatric adverse events compared with placebo.
- Use of CHANTIX was not associated with an increased risk of clinically significant NPS adverse events in the composite safety endpoint compared with bupropion or NRT

<table>
<thead>
<tr>
<th>Non-psychiatric cohort, N</th>
<th>Varenicline</th>
<th>Bupropion</th>
<th>NRT</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite endpoint: Number of patients with clinically significant NPS AEs, n (%)</td>
<td>30 (3.1%)</td>
<td>34 (3.5%)</td>
<td>33 (3.3%)</td>
<td>40 (4.1%)</td>
</tr>
<tr>
<td>Serious NPS, n (%)</td>
<td>1 (0.1%)</td>
<td>5 (0.5%)</td>
<td>1 (0.1%)</td>
<td>4 (0.4%)</td>
</tr>
<tr>
<td>Psychiatric Hospitalizations, n (%)</td>
<td>1 (0.1%)</td>
<td>2 (0.2%)</td>
<td>0 (0.0%)</td>
<td>1 (0.1%)</td>
</tr>
</tbody>
</table>
Neuropsychiatric Safety Study Results
Psychiatric Cohort

In the psychiatric cohort:

- There were more clinically significant neuropsychiatric (NPS) AEs reported in each treatment group compared with the non-psychiatric cohort.
- The incidence of events was higher for each of the active treatments compared to placebo.

<table>
<thead>
<tr>
<th></th>
<th>Varenicline</th>
<th>Bupropion</th>
<th>NRT</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychiatric cohort, N</td>
<td>1007</td>
<td>1004</td>
<td>995</td>
<td>997</td>
</tr>
<tr>
<td>Composite endpoint:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients with</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>clinically significant NPS AEs, n (%)</td>
<td>123 (12.2%)</td>
<td>118 (11.8%)</td>
<td>98 (9.8%)</td>
<td>95 (9.5%)</td>
</tr>
<tr>
<td>Serious NPS, n (%)</td>
<td>6 (0.6%)</td>
<td>8 (0.8%)</td>
<td>4 (0.4%)</td>
<td>6 (0.6%)</td>
</tr>
<tr>
<td>Psychiatric Hospitalizations, n (%)</td>
<td>5 (0.5%)</td>
<td>8 (0.8%)</td>
<td>4 (0.4%)</td>
<td>2 (0.2%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Composite Endpoint Comparison</th>
<th>Risk Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varenicline vs placebo</td>
<td>2.7 (-0.05, 5.4)</td>
</tr>
<tr>
<td>Bupropion vs placebo</td>
<td>2.2 (-0.5, 4.9)</td>
</tr>
<tr>
<td>NRT vs placebo</td>
<td>0.4 (-2.2, 3.0)</td>
</tr>
</tbody>
</table>
**Neuropsychiatric Safety Study**

**Common Adverse Events**

- The most common AEs were similar to those observed in premarketing studies.

**Adverse Events** (≥10% of varenicline subjects in the entire study population):
  - Nausea (25% varenicline vs. 7% on placebo)
  - Headache (12% varenicline vs. 10% on placebo).

**Psychiatric Adverse Events** (≥2% of patients in either treatment group by cohort).

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Non-psych Cohort</th>
<th>Psychiatric Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>varenicline</td>
<td>placebo</td>
</tr>
<tr>
<td>abnormal dreams</td>
<td>8%</td>
<td>4%</td>
</tr>
<tr>
<td>agitation</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>anxiety</td>
<td>5%</td>
<td>6%</td>
</tr>
<tr>
<td>depressed mood</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>insomnia</td>
<td>10%</td>
<td>7%</td>
</tr>
<tr>
<td>irritability</td>
<td>3%</td>
<td>4%</td>
</tr>
<tr>
<td>sleep disorder</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>depression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>nervousness</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Chantix USPI, Pfizer Inc., December 2016
In both cohorts, subjects treated with CHANTIX had a superior rate of CO-confirmed abstinence during weeks 9-12 and 9-24 compared to subjects treated with bupropion, nicotine patch and placebo.

Adapted from Chantix USPI, Pfizer Inc., December 2016
Important Safety information from Chantix® (varenicline) Label
Summary of Warnings & Precautions

- **Neuropsychiatric Adverse Events**
  Postmarketing reports of serious or clinically significant neuropsychiatric adverse events have included changes in mood (including depression and mania), psychosis, hallucinations, paranoia, delusions, homicidal ideation, aggression, hostility, agitation, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed suicide. Observe patients attempting to quit smoking with CHANTIX for the occurrence of such symptoms and instruct them to discontinue CHANTIX and contact a healthcare provider if they experience such adverse events. (Section 5.1)

- **Seizures**
  New or worsening seizures have been observed in patients taking CHANTIX. CHANTIX should be used cautiously in patients with a history of seizures or other factors that can lower the seizure threshold. (Section 5.2)

- **Interaction with Alcohol**
  Increased effects of alcohol have been reported. Instruct patients to reduce the amount of alcohol they consume until they know whether CHANTIX affects them. (Section 5.3)

- **Accidental Injury**
  Accidental injuries (e.g., traffic accidents) have been reported. Instruct patients to use caution driving or operating machinery until they know how CHANTIX may affect them. (Section 5.4)

- **Cardiovascular Events**
  A meta-analysis of 15 clinical trials, including a trial in patients with stable cardiovascular (CV) disease, demonstrated that while cardiovascular events were infrequent overall, some were reported more frequently in patients treated with CHANTIX. These events occurred primarily in patients with known cardiovascular disease. In both the clinical trial and meta-analysis, all-cause and cardiovascular mortality was lower in patients treated with CHANTIX. Instruct patients to notify their healthcare providers of new or worsening cardiovascular symptoms and to seek immediate medical attention if they experience signs and symptoms of myocardial infarction (MI) or stroke. (Sections 5.5 and 6.1)
**Somnambulism**
Cases of somnambulism have been reported in patients taking CHANTIX. Some cases described harmful behavior to self, others, or property. Instruct patients to discontinue CHANTIX and notify their healthcare provider if they experience somnambulism. (Sections 5.6 and 6.2)

**Angioedema and Hypersensitivity Reactions**
Such reactions, including angioedema, infrequently life-threatening, have been reported. Instruct patients to discontinue CHANTIX and immediately seek medical care if symptoms occur. (Sections 5.7 and 6.2)

**Serious Skin Reactions**
Rare, potentially life-threatening skin reactions have been reported. Instruct patients to discontinue CHANTIX and contact a healthcare provider immediately at first appearance of skin rash with mucosal lesions. (Sections 5.8 and 6.2)

**Nausea**
Nausea is the most common adverse reaction (up to 30% incidence rate). Dose reduction may be helpful. (Section 5.9)