Chantix Label Update

Chantix® (varenicline)
Prescribing Information
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Please refer to the full Prescribing Information on important treatment considerations for CHANTIX via the following link: https://www.pfizermedicalinformation.com/en-us/chantix  In the event this link does not work, please access the product’s approved Prescribing Information at www.pfizer.com/products.

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

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

Key USPI changes regarding neuropsychiatric (NPS) safety:

- Removal of the boxed warning regarding serious neuropsychiatric events.
- The corresponding warning regarding neuropsychiatric (NPS) adverse events was retained and updated.

Please refer to the complete Prescribing Information for details concerning the label updates and other important treatment considerations related to varenicline.
Chantix US Label Updates

- December 2016 Label Update
  - Neuropsychiatric Safety History, Label Update and FDA Statements
  - EAGLES Study

- June 2018 Label Update
  - Cardiovascular Safety
  - Data on Use in Pregnancy

- February 2019 Label Update
  - Pediatric Use

- Current Warnings and Precautions Summary
Neuropsychiatric (NPS) Safety Data of CHANTIX has Accumulated

- **2007-2009**
  - NPS Signal identified: Warning and Boxed Warning added to label;

- **2009-2010**
  - FDA Requires EAGLES Study and provides input into study design

- **2014**
  - Increased risk not identified: Results of RCT analyses and observational studies added to label but Boxed Warning retained

- **2016**
  - Evidence supports Boxed Warning removal

**Analyses of RCTs**

**Observational studies**

**Results from EAGLES Study**
- Specifically designed RCT to evaluate NPS safety

**Level of Evidence**
- LOW
- HIGH

**Post marketing reports**

**RCT** = Randomized Controlled Trial
December 2016 CHANTIX NPS Label Updates

- Boxed Warning regarding serious neuropsychiatric (NPS) adverse events was removed
- Corresponding warning regarding NPS adverse events was retained and updated
  - Includes new healthcare provider guidance on evaluating the risks and benefits of continuing treatment with CHANTIX in patients who experience NPS symptoms to consider options including dose reduction, continued treatment under closer monitoring, or discontinuing treatment.
- Safety and efficacy data from the EAGLES Study was included
CHANTIX® (varenicline) USPI: Removed Boxed Warning

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)]

Chantix USPI, Pfizer Inc, October 2014.
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.

See Chantix USPI Section 5.1 for more info
FDA revises description of mental health side effects of the stop-smoking medicines Chantix (varenicline) and Zyban (bupropion) to reflect clinical trial findings

Based on a U.S. FDA review of a large clinical trial (EAGLES) that we required the drug companies to conduct*:

- We have determined the risk of serious side effects on mood, behavior, or thinking with the stop-smoking medicines Chantix (varenicline) and Zyban^ (bupropion) is lower than previously suspected.

- The risk of these mental health side effects is still present, especially in those currently being treated for mental illnesses such as depression, anxiety disorders, or schizophrenia, or who have been treated for mental illnesses in the past.

- However, most people who had these side effects did not have serious consequences such as hospitalization.

- The results of the trial confirm that the benefits of stopping smoking outweigh the risks of these medicines.

^ Zyban is a registered trademark of GlaxoSmithKline plc.


EAGLES Study
The Largest Pharmacotherapy Study in Smoking Cessation

Randomized, Double-Blind, Active-Controlled (Nicotine patch) and Placebo-Controlled Study in About 8000 Participants\textsuperscript{1*}

Patient Population (N=7915)
- Aged 18–75 years
- Smoking ≥10 cigarettes per day
- ~Half without a history of psychiatric disorders
- ~Half with past or current stable psychiatric disorders

Randomization 1:1:1:1
- CHANTIX 1 mg BID
- Bupropion SR 150 mg BID
- Nicotine patch 21 mg/day
- Placebo

Patients were treated for 12 weeks and followed for another 12 weeks post-treatment

Composite Safety Endpoint: Patients with one or more clinically significant, of 17 specified neuropsychiatric (NPS) adverse events

\textsuperscript{1*} Patients received up to 10 minutes of counseling at each clinic visit.\textsuperscript{1,2}

EAGLES = Evaluating Adverse Events in a Global Smoking Cessation Study; BID = twice daily; SR = sustained release

EAGLES is referred to as the Postmarketing Neuropsychiatric Safety Outcome Trial in the USPI

Chantix USPI, Pfizer Inc., June 2018
EAGLES Study – Composite Endpoint: Clinically Significant NPS Adverse Events

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

- Anxiety
- Depression
- Feeling abnormal
- Hostility
- Agitation
- Aggression
- Delusions
- Hallucinations
- Homicidal ideation
- Mania
- Panic
- Paranoia
- Psychosis
- Irritability
- Suicidal ideation
- Suicidal behavior
- Completed suicide

*Occurring during or within 30 days following study drug treatment
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></th>
<th>Varenicline</th>
<th>Bupropion</th>
<th>NRT</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-psychiatric cohort, N</td>
<td>975</td>
<td>968</td>
<td>987</td>
<td>982</td>
</tr>
<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>
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><strong>Composite endpoint:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients with 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>
EAGLES 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):

<table>
<thead>
<tr>
<th></th>
<th>Varenicline (n=1982)</th>
<th>Placebo (n = 1979)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>25%</td>
<td>7%</td>
</tr>
<tr>
<td>Headache</td>
<td>12%</td>
<td>10%</td>
</tr>
</tbody>
</table>

**Psychiatric Adverse Events** (≥ 2% in any treatment group)

<table>
<thead>
<tr>
<th></th>
<th>Non-psych Cohort</th>
<th>Psychiatric Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Varenicline n=975</td>
<td>Placebo n=982</td>
</tr>
<tr>
<td></td>
<td>Varenicline n=1007</td>
<td>Placebo n=997</td>
</tr>
<tr>
<td>abnormal dreams</td>
<td>8%</td>
<td>4%</td>
</tr>
<tr>
<td></td>
<td>12%</td>
<td>5%</td>
</tr>
<tr>
<td>agitation</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td>anxiety</td>
<td>5%</td>
<td>6%</td>
</tr>
<tr>
<td></td>
<td>8%</td>
<td>6%</td>
</tr>
<tr>
<td>depressed mood</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>insomnia</td>
<td>10%</td>
<td>7%</td>
</tr>
<tr>
<td></td>
<td>9%</td>
<td>7%</td>
</tr>
<tr>
<td>irritability</td>
<td>3%</td>
<td>4%</td>
</tr>
<tr>
<td></td>
<td>5%</td>
<td>7%</td>
</tr>
<tr>
<td>sleep disorder</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>depression</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>nervousness</td>
<td>2%</td>
<td>3%</td>
</tr>
</tbody>
</table>

Adapted from Chantix USPI, Pfizer Inc., June 2018
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.
June 2018 CHANTIX Key Content Label Updates

- Cardiovascular (CV) Safety Warning was revised
  - CV safety data from EAGLES plus a non-treatment extension were added to the label

- Revised statements regarding risks in pregnancy
  - Information from an observational cohort study and smaller epi studies in pregnant women were added
## EAGLES plus non-treatment extension

**Primary CV Endpoint: MACE**

<table>
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<tr>
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</thead>
<tbody>
<tr>
<td><strong>During treatment</strong>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hazard Ratio (95% CI)</strong> vs. placebo</td>
<td>0.24 (0.03, 2.18)</td>
<td>0.49 (0.09, 2.69)</td>
<td>0.24 (0.03, 2.18)</td>
<td></td>
</tr>
<tr>
<td><strong>Through end of study</strong>**</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hazard Ratio (95% CI)</strong> vs. placebo</td>
<td>0.36 (0.10, 1.36)</td>
<td>1.09 (0.42, 2.83)</td>
<td>0.74 (0.26, 2.13)</td>
<td></td>
</tr>
</tbody>
</table>

**MACE**: Major Adverse Cardiovascular Events which included CV death, nonfatal myocardial infarction or nonfatal stroke

[IR] indicates incidence rate per 1000 person-years

* during treatment in the parent neuropsychiatric safety study

** either the end of the extension study or the end of parent neuropsychiatric safety study for those subjects not enrolled into the extension study
**EAGLES plus non-treatment extension**

Secondary CV Endpoints: MACE+ and All-cause mortality

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>During treatment</strong>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause deaths, n [IR]</td>
<td>0</td>
<td>2 [4.9]</td>
<td>0</td>
<td>2 [4.9]</td>
</tr>
<tr>
<td><strong>Through end of study</strong>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MACE+: CV death, nonfatal myocardial infarction, nonfatal stroke during treatment, a new onset or worsening peripheral vascular disease (PVD) requiring intervention, a need for coronary revascularization, or hospitalization for unstable angina

[IR] indicates incidence rate per 1000 person-years

* during treatment in the parent neuropsychiatric safety study

** either the end of the extension study or the end of the parent neuropsychiatric safety study for those subjects not enrolled into the extension study
Key CV Safety Label Updates

- CV outcome analysis from EAGLES plus non treatment extension were added
  
  **Conclusion**: Few MACE events occurred during the trial; therefore, the findings did not contribute substantively to the understanding of CV risk with CHANTIX

- Summary of revised CV safety warning:
  
  Patients with underlying cardiovascular (CV) disease may be at increased risk of CV events; however, these concerns must be balanced with the health benefits of smoking cessation.
  
  Instruct patients to notify their healthcare providers of new or worsening CV symptoms and to seek immediate medical attention if they experience signs and symptoms of MI or stroke.

See Chantix USPI Sections 5.5 & 14.10 for more info
Observational Pregnancy Cohort Study

Table 6. Summary of Primary and Secondary Outcomes for Three Birth Cohorts

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Varenicline Cohort (n=335)</th>
<th>Smoking Cohort (n=78,412)</th>
<th>Non-Smoking Cohort (n=806,438)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major congenital malformation*</td>
<td>12 / 334 (3.6%)</td>
<td>3,382 / 78,028 (4.3%)</td>
<td>33,950 / 804,020 (4.2%)</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>1 (0.3%)</td>
<td>384 (0.5%)</td>
<td>2,418 (0.3%)</td>
</tr>
<tr>
<td>Small for gestational age</td>
<td>42 (12.5%)</td>
<td>13,433 (17.1%)</td>
<td>73,135 (9.1%)</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>25 (7.5%)</td>
<td>6,173 (7.9%)</td>
<td>46,732 (5.8%)</td>
</tr>
<tr>
<td>Premature rupture of membranes</td>
<td>12 (3.6%)</td>
<td>4,246 (5.4%)</td>
<td>30,641 (3.8%)</td>
</tr>
<tr>
<td>Sudden infant death syndrome **</td>
<td>0/307 (0.0%)</td>
<td>51/71,720 (0.1%)</td>
<td>58/755,939 (&lt;0.1%)</td>
</tr>
</tbody>
</table>

* Included only live births in the cohorts. Prevalence among first trimester varenicline-exposed pregnancies (11/317 [3.5%]).
** There was a lag in death data in Denmark, so the cohorts were smaller.

- Other small epidemiological studies of pregnant women exposed to varenicline also did not identify an association with major malformations.
Varenicline in Pregnancy Summary

- Available data have not suggested an increased risk for major birth defects following exposure to varenicline in pregnancy, compared with women who smoke.
- Overall, available studies cannot definitely establish or exclude any varenicline-associated risk during pregnancy.
- Smoking during pregnancy is associated with maternal, fetal, and neonatal risks.

See Chantix USPI Section 8.1 for more info.
February 2019 Label Update: Pediatric Use
Double blind, Placebo-controlled RCT in Adolescent Patients

- **Population** (n=312): 12-19 year olds smoking ≥5 cigarettes/day, Fagerstrom score ≥4, ≥1 previous failed quit attempt

- **Treatment**
  - Randomized to one of two doses of varenicline adjusted by weight or placebo. Medication treatment continued for 12 weeks.
  - Patients were followed for an additional 40 weeks and received counselling throughout the study.

- **Results**:
  - Varenicline did not improve abstinence at weeks 9-12 compared to placebo.
  - The varenicline safety profile in this study was consistent with that observed in adult studies.

CHANTIX is **not recommended for use in pediatric patients 16 years of age or younger** because its efficacy in this population was not demonstrated.

Please see USPI section 8.4 for more information.
**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**
Patients with underlying cardiovascular (CV) disease may be at increased risk of CV events; however, these concerns must be balanced with the health benefits of smoking cessation. Instruct patients to notify their healthcare providers of new or worsening CV 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)
Important Safety information from Chantix® (varenicline) Label
Highlights of Warnings & Precautions (continued)

- **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)