by non-vaccine HPV types.  

**Anaphylactic Reactions:** As with all injectable vaccines, appropriate medical treatment should be readily available in case of rare anaphylactic reactions following the administration of the vaccine.

**Fever:** The decision to administer or delay vaccination because of a current or recent febrile illness depends largely on the severity of the symptoms and their etiology. Low-grade fever itself and mild upper respiratory infection are not generally contraindications to vaccination.

**Immunosuppression:** Individuals with impaired immune responsiveness, whether a result of the use of immunosuppressive therapy, a genetic defect, human immunodeficiency virus (HIV) infection, or other causes, may have a reduced antibody response to active immunization.

**Hematological Disorders:** As with intramuscular injections, this vaccine should not be given to individuals with bleeding disorders (e.g., hemophilia or thrombocytopenia) or to patients receiving anticoagulant therapy unless the potential benefits clearly outweigh the risks. If the vaccine is administered to such persons, it should be given with instructions to avoid the risk of hematoma following the injection.

**Drug Interactions:**

**Use with Other Vaccines:** Clinical studies indicate that this vaccine may be administered concomitantly (at a separate injection site) with hepatitis B vaccine (recombinant). Co-administration of this vaccine with other vaccines has not been studied.

**Use with Hormonal Contraceptives:** In clinical studies, 13,293 subjects (6,644 subjects receiving the vaccine and 6,649 subjects receiving placebo) who had follow-up visits after seven months used hormonal contraceptives, for a total of 17,597 person-years (65.1% of the total follow-up time in the study for these subjects). The use of the contraceptives or the lack thereof among the study participants did not alter the vaccine’s efficacy in this group using personal protective equipment (PPE).

**Use with Systemic Immunosuppressive Medication:** Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids, when used in greater than physiologic doses, may reduce the immune response to vaccines.

**Dosage and Administration:** Gardasil is given intramuscularly as three separate 0.5-ml doses: (1) at the elected date, (2) two months after the first dose, and (3) six months after the first dose.

The vaccine is injected into the deltoid region of the upper arm or in the higher anterolateral area of the thigh; it should not be injected intravascularly. Subcutaneous and intradermal administration have not been studied, and these techniques are therefore not recommended.

The prefilled syringe is intended for a single use only and for only one person. Single-use vials and a separate sterile
syringe and needle must be used for each individual.

Commentary: Gardasil is the first vaccine approved by the Food and Drug Administration (FDA) to prevent cervical cancer and vulvar and vaginal precancers caused by HPV types 16 and 18 and to prevent low-grade and precancerous lesions and genital warts caused by types 6, 11, 16, and 18. It represents a major health breakthrough because it is the first vaccine designed to prevent cancer. In clinical studies, the vaccine prevented 100% of HPV 16–related and HPV 18–related cervical cancers in women who had not been previously exposed to the relevant HPV types. It also prevented 99% of cases of genital warts caused by HPV 6 and 11.

In the U.S., approximately 10,000 cases of cervical cancer are diagnosed every year, and an average of 10 patients with the disease die each day. HPV types 16 and 18 account for approximately 70% of cases of cervical cancer, AIS, CIN stage 3, VIN stages 2 and 3 and VaIN stages 2 and 3. These types account for 50% of CIN 2 lesions. HPV 6 and 11 cause approximately 90% of cases of genital warts. Types 6, 11, 16, and 18 also cause 35% to 50% of all low-grade cervical, vaginal, and vulvar lesions (CIN I, VIN I, and VaIN I).

The vaccine does not reverse existing infections and does not seem to protect against the strains that account for the remaining 30% of cervical cancer cases. For sexually active patients, Pap smears may still show abnormalities that must be investigated. It can take decades for HPV infections to progress to cancer, and it may take that long to measure the benefits of the vaccine.


Bupropion HCl XL (Wellbutrin XL)

Manufacturer: GlaxoSmithKline, Research Triangle Park, NC

Indication: Bupropion XL extended-release tablets are now approved to prevent major depressive episodes in adult patients with a history of seasonal affective disorder (SAD).

Drug Class: This antidepressant of the amino ketone class is not chemically related to tricyclic and tetracyclic agents, selective serotonin reuptake inhibitors (SSRIs), or other known antidepressant agents. Its structure closely resembles that of diethylpropion; it is related to phenylethylamines. It is designated as (±)-1-(3-chlorophenyl)-2-[(1,1-dimethylethyl) amino]-1-propanone HCl.

Uniqueness of Drug: The extended-release form is indicated only for patients who meet strict diagnostic criteria for SAD, including a seasonal pattern of recurrent, clinically significant depressive symptoms with associated impaired functioning.

Boxed Warning:

Suicidality in Children and Adolescents. Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies of children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of bupropion XL or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber.

Bupropion XL is not approved for use in children.

Pooled analyses of short-term (four to 16 weeks) placebo-controlled trials of nine antidepressant drugs (SSRIs and others) in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these 24 trials, which involved more than 4,400 patients.

Warnings:

Clinical Worsening and Suicide Risk: Both children and adults with MDD may experience worsening of depression or the emergence of suicidal ideation and behavior or unusual changes in behavior, whether or not they are taking antidepressant medications. This risk may persist until significant remission occurs. There has been a long-standing concern that antidepressants may induce worsening of depression and the emergence of suicidality in some patients. In short-term studies, antidepressants did increase the risk of suicidal thinking and behavior in children and adolescents with MDD and other psychiatric disorders.

In trials of the nine antidepressant drugs alluded to in the boxed warning and mentioned above, there was considerable variation in risk among drugs but a tendency toward an increase for almost all drugs studied. The risk of suicidality was most consistently observed in the MDD trials, but there were signals of risk arising from some trials in other psychiatric indications (OCD and Social Anxiety Disorder) as well.

No suicides occurred in the trials. It is unknown whether the suicide risk in pediatric patients extends to longer-term use (beyond several months) and whether the risk extends to adults.

All pediatric patients receiving antidepressants for any indication should be observed closely, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Observations include at least weekly face-to-face contact with patients or their family members or caregivers during the first four weeks of treatment, followed by every-other-week visits for the next four weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may be appropriate between face-to-face visits.

Adults with MDD or comorbid depression in the setting of other psychiatric illness who are taking antidepressants should also be closely observed, especially during the initial few months of a course of drug therapy, or at times of a change in dose, either an increase or decrease.

Patients with a history of suicidal behavior or thoughts, patients exhibiting suicidal ideation before beginning treatment, and young adults are at an increased risk of suicidal thoughts or suicide attempts. All of these patients should receive careful monitoring during treatment.
Anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania have been reported in adults and children using antidepressants for MDD as well as for other psychiatric and nonpsychiatric indications. Although a causal link between the emergence of such symptoms and the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Healthcare providers should consider changing the therapeutic regimen and perhaps discontinuing the medication in patients whose depression is persistently worse or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or if they have not been present previously.

Families and caregivers of pediatric patients who are using antidepressants for MDD or other psychiatric and nonpsychiatric indications should be alerted to the need to watch for agitation, irritability, unusual changes in behavior, and suicidality; they should report any of these symptoms immediately to the patient's healthcare provider.

To reduce the risk of overdose, healthcare providers should prescribe bupropion XL tablets in the smallest quantity consistent with good patient management. Families and caregivers of adults being treated for depression should be similarly advised.

**Screening for Bipolar Disorder:** A major depressive episode may be the initial presentation of bipolar disorder. It is believed, although not established in controlled trials, that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described earlier represent such a conversion is unknown. However, before antidepressant treatment begins, patients with depressive symptoms should be screened to determine whether they are at risk for bipolar disorder. Screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and/or depression.

Bupropion XL is not approved for bipolar depression.

**Seizures:** Bupropion is associated with a dose-related risk of seizures. The risk of seizures is also related to patient factors, clinical situations, and concomitant medications, which must be considered in the selection of patients for therapy with bupropion XL. Bupropion XL therapy should be discontinued and not restarted in patients who experience a seizure during treatment.

Because bupropion XL is bioequivalent to both the immediate-release (IR) formulation and the sustained-release (SR) formulation, the incidence of seizures with bupropion XL, although not formally evaluated in clinical trials, may be similar to that for the IR and SR forms.

**Dose:** At doses up to 300 mg/day of the SR formulation, the incidence of seizure was approximately 0.1% (1/1,000). For IR bupropion, the incidence of seizure was approximately 0.4% in patients taking 300 to 450 mg/day; this incidence may exceed that of some other marketed antidepressants. The data on the IR form also suggest that the estimated seizure incidence increased almost 10-fold at doses between 450 and 600 mg/day.

The 600-mg dose is twice the usual adult dose, and 1.33 times the maximum recommended daily dose (450 mg) of bupropion XL tablets. This disproportionate increase in seizure incidence with dose increases calls for caution in dosing.

**Patient Factors:** Predisposing factors that may increase the risk of seizure with bupropion use include a history of head trauma or prior seizure, central nervous system (CNS) tumors, the presence of severe hepatic cirrhosis, and concomitant medications that lower seizure threshold.

**Clinical Situations:** Circumstances associated with an increased risk of seizures include the excessive use of alcohol or sedatives (e.g., benzodiazepines); an addiction to opiates, cocaine, or stimulants; the use of over-the-counter stimulants and anorectic agents; and the use of oral hypoglycemic agents or insulin for the treatment of diabetes.

**Concomitant Medications:** Many medications (e.g., antipsychotic agents, antidepressants, theophylline, and systemic steroids) are known to lower the seizure threshold.

**Reducing Seizure Risk:** A retrospective analysis of clinical experience gained during the development of bupropion suggests that the risk of seizure may be minimized (1) if the total daily dose of bupropion XL tablets does not exceed 450 mg and (2) if the rate of dose increases is gradual.

Bupropion XL should be administered with extreme caution to patients with a history of seizure, cranial trauma, or a predisposition toward seizures or patients being treated with other agents that lower the seizure threshold.

**Hepatic Impairment:** Bupropion XL should be used with extreme caution in patients with severe hepatic cirrhosis. In these patients, the frequency of the dose should be reduced, because peak bupropion levels as well as area-under-the-curve (AUC) concentrations are substantially increased; accumulation of the drug is likely to occur in such patients to a greater extent than usual. The dose should not exceed 150 mg every other day in hepatically impaired patients.

**Drug Interactions:** Patients should be made aware that bupropion XL contains the same active ingredient found in Zyban, which is used as an aid to help patients with smoking cessation. Bupropion XL should not be used in combination with Zyban or any other medications that contain bupropion (bupropion SR or bupropion IR).

**Dosage and Administration:** For preventing seasonal major depressive episodes associated with SAD, bupropion XL should generally be initiated in the autumn prior to the onset of depressive symptoms. Treatment should continue through the winter and should be tapered and discontinued in early spring.

The timing of initiation and the duration of treatment should be tailored to each patient based on the historical pattern of seasonal major depressive episodes. Patients whose seasonal depressive episodes are infrequent or not associated with significant impairment should not generally be treated prophylactically.

Dosing with bupropion XL should begin at 150 mg/day, given as a single daily dose in the morning. If the 150-mg initial dose is adequately tolerated, the dose should be increased to 300 mg/day after one week. If the 300-mg dose is not adequately tolerated, the dose can be reduced to 150 mg/day.

The usual adult target dose for bupropion XL tablets is...
Varenicline Tartrate (Chantix)  
**Manufacturer:** Pfizer, New York, NY  
**Indication:** Varenicline is indicated as an aid in smoking cessation.  
**Drug Class:** As the tartrate salt, varenicline is a white to off-white to slightly yellow solid powder with the chemical name of 7,8,9,10-tetrahydro-6,10-methano-6H-pyrazino[2,3-h][3]benzazepine, (2R,3R)-2,3-dihydroxybutanedioate (1:1). It is not a controlled substance.  
**Uniqueness of Drug:** Varenicline binds at sites in the brain with a high affinity and selectivity at alpha4 beta2 neuronal nicotinic acetylcholine receptors. The efficacy of varenicline in smoking cessation is believed to be the result of its activity at a subtype of the nicotinic receptor, where its binding produces agonist activity while simultaneously preventing nicotine binding to alpha4 beta2 receptors. The drug may help patients in two ways: (1) by providing some nicotine effects to ease the withdrawal symptoms and (2) by blocking the effects of nicotine from cigarettes if patients resume smoking.  
**Precautions:** Physiological changes resulting from smoking cessation, with or without treatment with varenicline, may alter the pharmacokinetics or pharmacodynamics of some drugs (e.g., theophylline, warfarin, insulin). As a result, an adjustment in the dosage of bupropion XL might be necessary.  
**Drug Interactions:** On the basis of varenicline’s characteristics and clinical experience to date, no clinically meaningful pharmacokinetic drug interactions have been observed.  
**Adverse Drug Events:** ADEs associated with varenicline at a rate greater than 5% and at twice the rate with placebo included nausea, sleep disturbance, constipation, flatulence, and vomiting. Nausea was generally described as mild or moderate and often transient; for some subjects, however, it persisted for several months. The incidence of nausea was dose-dependent. Initial titration of the dose was beneficial in reducing nausea. Nausea was reported by approximately 30% of patients treated with varenicline 1 mg twice daily after an initial week of dose titration. With varenicline 0.5 mg twice daily, the incidence of nausea was 16% after the initial titration. Approximately 3% of subjects using varenicline 1 mg twice daily in studies involving 12 weeks of treatment stopped treatment prematurely because of nausea. For patients with intolerable nausea, a dose reduction should be considered.  
**Dosage and Administration:** Smoking-cessation therapies are more likely to succeed for patients who are motivated to stop smoking and who are provided with additional advice and support. Patients should be given appropriate educational materials and counseling to support their attempts to quit. Patients should be encouraged to set a date to stop smoking, and they should begin varenicline therapy one week before this date. Varenicline should be taken after eating and with a full glass of water. The recommended dose is 1 mg twice daily after a one-week titration period, as follows:  
- days one to three: 0.5 mg once daily  
- days four to seven: 0.5 mg twice daily  
- day eight to the end of treatment: 1 mg twice daily  

For patients who cannot tolerate ADEs after taking varenicline, the dose can be reduced temporarily or permanently. Patients should use varenicline for 12 weeks. For patients who have successfully stopped smoking at the end of 12 weeks, an additional course of 12 weeks of treatment with varenicline is recommended to enhance the likelihood of long-term abstinence.  

Patients who do not succeed in stopping smoking during 12 weeks of initial therapy or who relapse after treatment should be encouraged to try again after factors contributing to the failed attempt have been identified and addressed.  
**Commentary:** Varenicline is designed to partially activate the nicotinic receptor and to reduce the severity of cravings and nicotine-withdrawal symptoms. If a person smokes a cigarette while receiving treatment, varenicline has the potential to diminish the sense of satisfaction associated with smoking. This may help to prevent the cycle of nicotine addiction.  

The advent of varenicline represents ground-breaking science, leading to the first prescription treatment aimed directly at smoking cessation in nearly a decade. Nicotine affects nearly every organ in the body. Smoking is responsible for approximately one in five deaths in the U.S. and costs the health care system about $167 billion annually.  
**Sources:** www.pfizer.com; www.fda.gov/bbs/topics/NEWS/2006/NEW01370.html; www.cdc.gov