

# What's New in Clinical Pharmacology and Therapeutics

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## ABSTRACT

The US Food and Drug Administration (FDA) has approved several new drugs in the past 2 years. This article provides an overview of some of the newer drugs that are likely to find wider use in the future. The drugs reviewed in this article can be used to treat cardiovascular system problems, diabetes mellitus, multiple sclerosis, hepatitis B infection, hyponatremia, Parkinson's disease, rheumatoid arthritis, pain, constipation, and insomnia. Another drug discussed can be used to help a patient stop smoking. The article also discusses Gardasil, the recombinant vaccine against human papilloma virus (types 6, 11, 16, and 18).

## INTRODUCTION

Several new drugs have been approved by the US Food and Drug Administration (FDA) in the last 2 years. The following is a summary of some of the newer agents that are likely to find wider use in treatment of various disorders in the next few years. The article refers to the safety of these drugs in pregnancy based on toxicity to the fetus in animal and human studies. Category A drugs are safe to use in pregnancy, B are probably safe, C are probably unsafe, D are unsafe, and X are definitely contraindicated. Not all drugs have been studied to assign a risk category.

The newly marketed drugs tend to be more expensive, particularly when they have a unique mode of action and their rare side effects take awhile to manifest. In general, the newer drugs should be used only if established drugs are ineffective or not tolerated by the patient.

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Studies comparing newer drugs with older, well-established drugs, particularly generic drugs, are initially hard to come by as the pharmaceutical manufacturers are reluctant to support such studies, lest their product proves inferior to the comparison drug. Eventually, comparison studies are performed by interested investigators and the comparative advantages and disadvantages of various drugs are determined.

Only 1000-3000 subjects are required in a trial to establish a drug's efficacy and seek the FDA's approval. Rare side effects that occur only once in 10,000 patients manifest after the drug is on the market and prescribed in millions of patients. If the drug causes serious or fatal toxicity, it is withdrawn from the market. Sometimes a manufacturer may withdraw the drug if it doesn't sell enough to justify continued marketing.

## CARDIOVASCULAR SYSTEM

### *Ranolazine (Ranexa)*

Ranolazine is a first selective late sodium current inhibitor approved for the treatment of chronic stable angina. It is the first new anti-anginal drug in more than 20 years. The inhibition of late sodium current results in a reduced intracellular sodium and calcium overload during myocardial ischemia. This causes inhibition of fatty acid oxidation and increases glucose oxidation generating more adenosine triphosphate (ATP) for each molecule of oxygen consumed and may decrease oxygen demand while maintaining myocardial contractility. It should be used in combination with other anti-anginal drugs such as beta-blockers, nitrates, or amlodipine as its effect may compliment the action of existing anti-anginal agents.<sup>1</sup> Ranolazine has been shown to be effective in increasing exercise treadmill test duration, with or without conventional anti-anginal treatment, in patients with chronic angina. The clinical benefit is consistent in patients with comorbidities such as chronic obstructive pulmonary disease (COPD), diabetes, low heart rate or blood pressure, prior myocardial infar-

tion, or revascularization. It does not lower blood pressure and heart rate. The common adverse effects include dizziness, headache, constipation, and nausea.<sup>2</sup>

Ranolazine has several drug interactions. It can increase the QT interval, a measure of the heart's electrical cycle that is determined by the heart rate, in a dose-dependant manner and can therefore increase the risk of arrhythmias. It is contraindicated in patients with pre-existing QT prolongation or together with QT prolonging drugs such as quinidine, sotalol, dofetilide, amiodarone, and erythromycin. It is mainly metabolized in the liver by CYP3A enzymes and, therefore, CYP3A inhibitors such as diltiazem, verapamil, ketoconazole, and grapefruit juice should not be co-administered with ranolazine since the risk of arrhythmias increases. Amlodipine does not inhibit CYP3A and can be used along with ranolazine. The dose of drugs such as simvastatin and digoxin should be decreased when ranolazine is simultaneously used. Ranolazine can increase blood pressure by as much as 15 mm Hg in patients with renal impairment. It is a pregnancy category C drug.

#### *Aliskiren (Tekturna)*

Aliskiren is the first of a new class of oral antihypertensives, the direct renin inhibitors.<sup>3-4</sup> It can be used as monotherapy or in combination with other antihypertensive agents. Aliskiren inhibits renin, thereby preventing conversion of angiotensinogen to angiotensin I, which is the first rate-limiting step in the renin-angiotensin-aldosterone system. This leads to decreased levels of angiotensin I, angiotensin II, and aldosterone and thus reduces arterial tone, renal sodium absorption, and aldosterone secretion—all resulting in decreased blood pressure. High-fat meals decrease absorption of aliskiren, and patients should establish a regular pattern of taking it either before or after meals. Dosage adjustment is not required in elderly patients or in those with mild to moderate renal or hepatic insufficiency.

The most common adverse effect is diarrhea, which is dose-related and occurs more in patients 65 years or older and in women. Cough occurs approximately a half to a third less often than with ACE inhibitors (ACEIs). Incidence of angioedema in studies is 0.06%. Other adverse effects are rash, elevated uric acid, gout, and renal stones. Hyperkalemia occurs less commonly when aliskiren is used as monotherapy. It is metabolized by cytochrome P450 3A4 and thus ketoconazole, which is a strong inhibitor of this enzyme, increases the aliskiren level by about 50%. Concurrent use of aliskiren with furosemide results in decreased serum concentration of furosemide, which could lead to a diminished

effect of furosemide. No clinically relevant drug interactions occur when aliskiren is used along with atenolol, digoxin, amlodipine, hydrochlorothiazide, and ramipril. Several clinical trials have shown aliskiren to be an effective antihypertensive when used as monotherapy; it causes reduction in blood pressure similar to irbesartan. The combination of hydrochlorothiazide and aliskiren lowers blood pressure more than monotherapy with either drug alone. In pregnancy, it is a category C drug during the first trimester and category D during the second and third trimester.

At the present time, it doesn't appear that aliskiren will have any advantage over ACEIs or angiotensin receptor blockers (ARBs). It is very unlikely that addition of aliskiren to ACEIs or ARBs will offer additional antihypertensive effect and it may increase toxicity.

## DIABETES MELLITUS

#### *Sitagliptin (Januvia)*

Sitagliptin is first in a new class of drugs called gliptins, which are inhibitors of the enzyme dipeptidyl-peptidase-4 (DPP-4). DPP-4 breaks down endogenous incretins, and gliptins such as sitagliptin inhibit this enzyme, increasing incretin hormone in the body. Incretin hormones increase insulin release in response to meals and decrease glucagon production in a glucose-dependent manner, lowering serum glucose concentrations. Sitagliptin has been approved for glucose control in patients with type 2 diabetes, and is to be used as monotherapy<sup>5</sup> or in combination with metformin or a glitazone (pioglitazone-Actos, rosiglitazone-Avandias). When taken orally, it is rapidly absorbed and excreted by the kidneys. Therefore the dose needs to be decreased in patients with moderate or severe renal disease. The most commonly reported adverse effects are symptoms of nasopharyngitis, upper respiratory infection, and headache. The incidence of hypoglycemia is no higher with sitagliptin than with placebo. Advantages of sitagliptin include lack of weight gain and low risk of hypoglycemia. Studies have shown that sitagliptin is less effective than sulfonylureas and metformin in lowering HbA1c.<sup>6</sup> It is a category B drug in pregnancy.

#### *Exenatide (Byetta)*

Exenatide is the first in a new class of antidiabetic drugs known as incretin mimetics.<sup>7</sup> It acts by stimulating glucagon-like peptide-1 (GLP-1) receptors, which causes stimulation of glucose-dependent insulin secretion, inhibits the release of glucagon after meals, and slows the rate of gastric emptying. It also suppresses appetite and

may aid in weight loss. It is a synthetic form of exendin found in the saliva of the Gila monster, which stimulates the pancreas. Exenatide is indicated as add-on therapy in patients with type 2 diabetes to improve glycemia when diabetes is not adequately controlled with oral hypoglycemic agents such as metformin and sulfonylureas.<sup>8</sup> It is not indicated as monotherapy. Exenatide is not a substitute for insulin in patients with type 1 diabetes. Its use in patients taking insulin, thiazolidinediones, meglitinides, or alpha-glucosidase inhibitors has not been studied.

It is administered subcutaneously in the thigh, abdomen, or upper arm. It should be taken twice daily, within 60 minutes of a morning and evening meal. The dose of sulfonylureas should be empirically decreased to reduce the risk of hypoglycemia, but this risk is less with metformin; hence the metformin dose does not have to be decreased. Other than hypoglycemia, adverse effects include nausea, vomiting, diarrhea, dizziness, headache, and dyspepsia, which are generally mild to moderate. Since exenatide is a protein molecule, antibodies may develop. However this does not affect the glycemic control significantly. Exenatide may affect the rate and extent of absorption of orally administered drugs as it slows gastric emptying.

Pre-filled pens are available, which can be kept at room temperature not to exceed 77° F for up to 30 days after the first use. The pen should be protected from light and should not be frozen. Exenatide is contraindicated in patients with severe renal impairment (creatinine clearance <30 ml/min) or those with end-stage renal disease. It should not be used in patients with gastroparesis. It is a pregnancy category C drug.

## **MULTIPLE SCLEROSIS**

### *Natalizumab (Tysabri)*

Natalizumab is one of the new disease-modifying therapies for a relapsing form of multiple sclerosis.<sup>9</sup> It was temporarily removed from the market due to side effects but is once again available; however its use is restricted. It is a recombinant humanized monoclonal antibody produced in murine myeloma cells. Natalizumab acts by binding to the glycoprotein alpha 4beta1-integrin, which is an important mediator of cell adhesion and transendothelial migration. This blocks cell adhesion and interferes with the migration of autoimmune leukocytes across the blood-brain-barrier, which may interrupt the inflammatory changes in multiple sclerosis. It is administered by intravenous infusion over 1 hour once every 4 weeks.

The most frequently reported adverse effects are head-

ache, fatigue, and arthralgias slightly higher than with the placebo. Severe adverse reactions include susceptibility to infections; hypersensitivity reactions include anaphylaxis and depression. Its use may also result in development of neutralizing antibodies to natalizumab, which is associated with loss of efficacy.<sup>10</sup> When interferon beta-1a is used along with natalizumab, the clearance of natalizumab is reduced by approximately 30%, which does not necessitate a dosage change. Results of any drug interactions with concurrent use of glatiramer are inconclusive. Studies have shown that use of natalizumab in multiple sclerosis results in a decrease in the number of relapses and new brain lesions. Its effect on disease progression is yet to be determined. It can be used as monotherapy or add-on therapy and should be considered for patients who cannot tolerate other therapies or have not benefited from other treatment options. It is a pregnancy category C drug.

## **HEPATITIS B INFECTION**

### *Telbivudine (Tyzeka)*

Telbivudine is the newest thymidine nucleoside analog approved by the FDA for the oral treatment of hepatitis B infection in patients 16 years or older.<sup>11</sup> It acts by blocking the hepatitis B virus (HBV) DNA polymerase, which is responsible for HBV infection in which there is evidence of active viral replication or persistent elevations in serum aminotransferases—alanine aminotransferase (ALT) or aspartate aminotransferase (AST), or histologically active hepatitis. Unlike lamivudine and adefovir, this drug has no known activity against human immunodeficiency virus (HIV) or other viruses. It is excreted by the kidneys; therefore the dose needs to be adjusted in patients with renal impairment. The most common adverse effects are fatigue, malaise, myopathy, diarrhea, gastritis, and headache. Patients should be cautioned not to discontinue treatment abruptly on their own because that may cause acute exacerbation of hepatitis B. Clinical studies have shown that telbivudine is more efficacious than lamivudine in HBeAg-positive patients and as effective as lamivudine in HBeAg-negative patients. Preliminary results from other trials have shown that telbivudine is also superior to adefovir. As is the case with other oral agents used in the treatment of hepatitis B infection, the role of telbivudine may be limited by the potential for hepatitis B viral resistance. Telbivudine is a pregnancy category B drug.

## **HYPONATREMIA**

### *Conivaptan (Vaprisol)*

Conivaptan is a vasopressin antagonist that has been

approved by the FDA for the short-term treatment of euvoletic hyponatremia in hospitalized patients.<sup>12</sup> Conivaptan acts by decreasing the permeability of vasopressin receptors in the renal collecting duct leading to excretion of free water. It is given intravenously after an initial bolus followed by a continuous infusion for up to 4 days if the response is inadequate in the first 24 hours. The most common adverse effects are infusion site reactions (50%), headache, thirst, hypokalemia, diarrhea, and orthostatic hypotension. Conivaptan inhibits CYP3A4 enzyme, therefore it is contraindicated with other CYP3A4 inhibitors such as itraconazole, clarithromycin, etc. It may cause rhabdomyolysis in patients taking statins. Overly rapid correction of serum sodium (ie, >12 meq/L/24 hours) may also occur and may result in neurologic complications due to osmotic demyelination. In patients with renal insufficiency, it can be used as an alternative to demeclocycline, which also inhibits the action of vasopressin but can cause nephrotoxicity. It is classified as category C drug for use during pregnancy.

### **PARKINSON'S DISEASE**

#### *Apomorphine (Apokyn)*

Apomorphine is a dopamine agonist indicated for treatment of advanced Parkinson's disease during periods of "hypomobility," so-called "off-periods."<sup>13</sup> During these periods, the patients become immobile or unable to perform activities of daily living. In a clinical trial, patients with hypomobility treated with apomorphine showed significant (62%) improvement in Parkinson's disease rating scores compared to no improvement with a placebo. Apomorphine is given subcutaneously and is rapidly absorbed, with onset of action within 10-20 minutes that lasts about 60 minutes. Apomorphine can cause severe nausea and vomiting and has to be discontinued in 2%-3% patients. Hence, an antiemetic such as trimethobenzamide (Tigan) should be started 3 days before starting apomorphine and continued for at least the first 2 months of treatment. Apomorphine is contraindicated with other antiemetics, the 5HT<sub>3</sub> antagonists such as ondansetron, because the combination can lead to severe hypotension and loss of consciousness. Also, dopamine antagonists like prochlorperazine (Compazine) or metoclopramide (Reglan) may antagonize effects of apomorphine and worsen Parkinson's symptoms. The most common adverse effects are yawning, dyskinesias, daytime sleep attacks, orthostatic hypotension, hallucinations, and peripheral edema. Hypersexuality and increased erections can also occur. Apomorphine is also

associated with increase in QT interval and should be avoided in conjunction with other drugs that can prolong QT interval.

### **RHEUMATOID ARTHRITIS**

#### *Abatacept (Orencia)*

Abatacept is the first in a new class of drugs approved for the treatment of rheumatoid arthritis. It selectively inhibits T-cell activation by blocking the interaction of CD80 and CD86 with CD28 required for T-cell activation.<sup>14</sup> This results in decreased serum concentrations of inflammatory markers, cytokines, and rheumatoid factor, which all play an important role in the pathogenesis of rheumatoid arthritis. Abatacept should be used in patients with moderate to severe rheumatoid arthritis who have not responded to tumor-necrosis factor (TNF) inhibitors<sup>15</sup> such as etanercept (Enbrel) or 1 or more disease-modifying anti-rheumatic drugs (DMARDs) such as anakinra (Kineret). It can be used as monotherapy or in combination with a DMARD but not with TNF-inhibitors or anakinra. It is given intravenously over 30 minutes. The most common adverse effects are headache, symptoms of nasopharyngitis, and nausea, but the most serious effects are infections and increased risk of malignancies. Patients should be tested for tuberculosis before starting treatment with abatacept and should not be given live vaccines while on treatment or afterward for 3 months. Patients treated concurrently with abatacept and TNF-inhibitors are at an increased risk for serious infections with no improved efficacy. Patients with COPD, treated with abatacept, may develop more adverse respiratory effects than with placebo. It is a pregnancy category C drug.

### **PAIN**

#### *Pregabalin (Lyrica)*

Pregabalin is the newest agent approved by the FDA for the treatment of neuropathic pain associated with post-herpetic neuralgia and diabetic peripheral neuropathy and for adjunctive treatment of partial onset seizures in epileptic patients. It is an analogue of gamma-aminobutyric acid (GABA) that binds selectively to the alpha2-delta subunit of the calcium channels resulting in a decrease of calcium influx at nerve terminal. This reduces the release of various neurotransmitters, including glutamate, norepinephrine, and substance P, which in turn results in its analgesic, anti-convulsant, and anxiolytic effects.<sup>16</sup>

The most common adverse effects include dizziness and somnolence. Other side effects include fatigue, dry mouth, peripheral edema, headache, and difficulty with

concentration/attention. It is excreted almost entirely unchanged in the urine. It does not interact with other anticonvulsants. Clinical studies in patients with post-herpetic neuralgia and diabetic peripheral neuropathy have shown that pregabalin treatment resulted in a significant decrease in mean pain score at the endpoint, compared to a placebo. Pregabalin is structurally similar to gabapentin but is more potent than gabapentin and achieves efficacy at lower doses, which may result in less fatigue and other side effects.<sup>17</sup> It may be indicated in patients who cannot tolerate other medication for neuropathic pain. The Drug Enforcement Administration (DEA) has classified pregabalin as a schedule V drug due to its potential for physical dependence.

### CONSTIPATION

#### *Lubiprostone (Amitiza)*

Lubiprostone is the first selective chloride channel activator approved for the treatment of chronic idiopathic constipation in all adults. It is an alternative for patients over 65 years for whom tegaserod is not indicated/approved. It activates CIC-2 chloride channels in the gastrointestinal tract leading to increased intestinal secretion and motility and improved stool consistency.<sup>18-19</sup> Lubiprostone should be used in patients with constipation who have not responded to use of fiber or laxatives. The common adverse effects include headache, nausea, and diarrhea. Nausea decreases with once daily dosing and when taken with food. Clinical trials have shown that lubiprostone increases bowel movements by approximately 3 per week. Study results were similar regardless of gender, age, or race. Studies have also reported continued efficacy in decreasing constipation severity, abdominal bloating, and discomfort for up to 1 year. Lubiprostone is a category C drug in pregnancy.

### INSOMNIA

#### *Ramelteon (Rozerem)*

Ramelteon is the first highly selective melatonin type 1 (MT1) and type 2 (MT2) receptor agonist approved for the treatment of insomnia in adults characterized by difficulty with sleep onset.<sup>20</sup> It is unlike other prescription hypnotics and is not a controlled substance. Ramelteon has no measurable affinity for the GABA receptor complex or for benzodiazepine, dopamine, or opiate receptors. There is no drug abuse potential or "hangover" effects like those often associated with other agents used to treat insomnia. Also, unlike zolpidem extended release (Ambien CR) and eszopiclone (Lunesta), ramelteon can be used long-term and is well tolerated in elderly patients. Its onset of action is approximately 30

minutes and patients should take it within 30 minutes of going to bed. The most commonly reported side effects are headache, dizziness, and somnolence. In 1 study, ramelteon increased serum prolactin level. Ramelteon undergoes extensive first-pass metabolism and is predominantly metabolized by the hepatic cytochrome P 450 isoenzyme 1A2. Fluvoxamine (Luvox) an SSRI, is a strong inhibitor of this enzyme and has been shown to markedly increase serum concentration of ramelteon, so the 2 drugs should not be used simultaneously. Ciprofloxacin is also a CYP1A2 inhibitor and may have similar effect. Rifampin, which induces CYP enzymes, significantly decreases serum levels of ramelteon when used with it concurrently. Clinical trials using polysomnography have shown that ramelteon decreases mean latency to persistent sleep by 7.5 to 15.7 minutes and increased total sleep time by 11.6 to 19 minutes compared to placebo.<sup>21</sup> Ramelteon is a pregnancy category C drug.

### SMOKING

#### *Varenicline (Chantix)*

Varenicline is the first partial nicotine agonist approved for smoking cessation in individuals older than 18 years of age.<sup>22</sup> It is an alpha-4-beta-2 nicotine acetylcholine receptor partial agonist and has greater affinity than nicotine but stimulates receptor-mediated activity at a significantly lower level than nicotine. This partial nicotine effect blocks the pleasurable effects of smoking and also decreases the withdrawal symptoms from nicotine. Varenicline is absorbed from gastric mucosa and is minimally metabolized and excreted unchanged by the kidneys, therefore the dose needs to be adjusted in patients with severe renal impairment (estimated creatinine clearance of <30 ml/min). The most common adverse effects are nausea, sleep disturbance, headaches, abnormal dreams, constipation, flatulence, and xerostomia. Nausea decreases when it is taken after eating and with a full glass of water.

Clinical studies have shown varenicline to be effective in reducing the urge to smoke and more patients maintained abstinence than with a placebo. Patients treated with varenicline also reported significantly greater decrease in craving and withdrawal symptoms compared to placebo-treated patients. It is also more effective than bupropion (Zyban) in increasing smoking cessation rates, but does not reduce the weight gain after smoking cessation that occurs in patients using bupropion. Patients should be advised to set a "target quit date" and varenicline should be started 1 week before that date and continued for 12 weeks. For patients who have success-

**Appendix. Summary of The Drugs Discussed**

<b>Drug</b>	<b>Indication</b>	<b>Pregnancy Adverse Effects</b>	<b>Category</b>	<b>Route/Comments</b>
Ranolazine (Ranexa)	Chronic stable angina	Dizziness, headache, constipation, can increase QT interval	C	Taken orally Does not decrease blood pressure and heart rate
Aliskiren (Tekturna)	Hypertension	Diarrhea, cough, gout	First trimester C Second and third trimester D	Taken orally
Sitagliptin (Januvia)	Type 2 diabetes mellitus	Nasopharyngitis, hypoglycemia, headache	B	Taken orally Advantage-lack of weight gain
Exenatide (Byetta)	Add-on therapy in treatment of Type 2 diabetes mellitus	Hypoglycemia, nausea, vomiting, dyspepsia, headache	C	Subcutaneous May aid in weight loss
Natalizumab (Tysabri)	Relapsing form of multiple sclerosis	Headache, fatigue, arthralgias	C	IV Infusion
Telbivudine (Tyzeka)	Hepatitis B infection	Fatigue, malaise, myopathy, gastritis	B	Taken orally
Conivaptan (Vaprisol)	Euvolumic Hyponatremia	Infusion site reactions, orthostatic hypotension, hypokalemia	C	Intravenous Alternate to Demeclocycline in patients with renal insufficiency with hyponatremia
Apomorphine (Apokyn)	Parkinsons' disease during periods of "hypomobility"	Dyskinesias, peripheral edema, nausea, vomiting		Subcutaneous Hypersexuality Can increase QT interval
Abatacept (Orencia)	Rheumatoid arthritis—moderate to severe	Nasopharyngitis, nausea, headache	C	Intravenous Increased risk of infections and malignancies
Pregabalin (Lyrica)	Neuropathic pain in post-herpetic neuralgia and diabetic peripheral neuropathy	Dizziness, somnolence		Taken orally Scheduled V drug (potential for physical dependence)
Lubiprostone (Amitiza)	Chronic constipation	Headache, nausea, diarrhea	C	Taken orally
1Ramelteon (Rozerem)	Insomnia	Headache, dizziness, somnolence	C	Taken orally No abuse potential Can be used long-term Well tolerated in elderly
Varenicline (Chantix)	Smoking cessation	Sleep disturbance, abnormal dreams, xerostomia	C	Taken orally
Human Papilloma Virus (Types 6, 11, 16, 18) Vaccine (Gardasil)	Prevention of diseases caused by Human Papilloma Virus (Types 6, 11, 16, 18)	Injection site reactions	B	Intramuscular Not indicated in the treatment of active genital warts, cervical carcinoma, etc
Herpes Zoster Vaccine (Zostavax)	Prevention of Herpes Zoster	Injection site reactions		Subcutaneous Contraindicated in immunocompromised patients and those on immunosuppressive therapy or those with active untreated tuberculosis

fully stopped smoking during the first 12 weeks, an additional course of 12 weeks is recommended to further increase the likelihood of long-term abstinence.<sup>23</sup> The safety and efficacy of co-administration of varenicline with other smoking cessation aids has not been established. Varenicline is a pregnancy category C drug.

## VACCINES

*Human Papilloma Virus (Types 6, 11, 16, and 18)*

*Recombinant Vaccine (Gardasil)*

Gardasil is the first vaccine approved for the prevention of human papilloma virus (HPV) types 6, 11, 16, and 18.<sup>24</sup> Approximately 95% of anogenital warts are caused by HPV types 6 and 11 and more than 70% of cervical cancers and high-grade cervical intraepithelial neoplasia (CIN) are caused by HPV types 16 and 18. It has no effect against non-vaccine HPV types, and infected women may develop sequela associated with non-vaccine HPV types. Hence, Gardasil does not eliminate the need for routine cervical screening. Gardasil acts by stimulation of antibody production in vivo against the above 4 types of HPV. It is indicated for females 9-26 years old. It is given as 0.5 ml intramuscularly in the deltoid region of the upper arm or in the higher anterolateral area of the thigh at 0, 2, and 6 months.

The most common adverse effects are injection site reactions including pain, swelling, erythema and pruritus, and fever. It can be given at the same time with a hepatitis B vaccine but at a different site. Patients should not be on immunosuppressive treatments such as antimetabolites, alkylating agents, cytotoxic agents, and corticosteroids or with impaired immune response such as in human immunodeficiency virus (HIV) infected patients since these can decrease the immune response to the vaccine. The vaccine is not indicated in the treatment of active genital warts, cervical cancer, or CIN. It is contraindicated in patients with bleeding disorders like hemophilia or thrombocytopenia or on anticoagulants because of the increased risk of bleeding and hematoma formation. In pregnancy, it is rated as a category B risk.

*Herpes Zoster Vaccine (Zostavax)*

Herpes zoster vaccine is a live attenuated vaccine approved for prevention of herpes zoster (shingles) in patients 60 years or older. This vaccine protects against the development of zoster by boosting cell-mediated immunity.<sup>25</sup> It is not indicated to treat herpes zoster or post-herpetic neuralgia. It is administered subcutaneously, as a single dose. The most common adverse effects are injection site reactions such as erythema, pain,

swelling, and pruritus. These are generally mild. This vaccine is contraindicated in persons who are immunocompromised, such as those with primary or acquired immunodeficiency including leukemia, lymphoma, or AIDS, or those receiving immunosuppressive therapy including high doses of corticosteroids (prednisone >20 mg/day), or cytotoxic chemotherapy. It is also not indicated in patients with a history of an anaphylactic reaction to gelatin, neomycin, or other components of the vaccine. Herpes zoster vaccine should not be given to patients with active, untreated tuberculosis.

Varicella (chickenpox) vaccine (Varivax) used in children to vaccinate against varicella and herpes zoster vaccine (Zostavax) to prevent herpes zoster in adults are not interchangeable as herpes zoster vaccine is 14 times more potent than varicella vaccine because higher potency is needed to elicit cell-mediated immunity in adults. A clinical study has demonstrated that herpes zoster vaccine decreases the risk of herpes zoster infection by half, reduces the severity and duration or pain and discomfort by 61%, and prevents post-herpetic neuralgia by 67%.

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