

# *The New Jersey* **JOURNAL of Pharmacy**

New Jersey Pharmacists Association

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### Mission Statement:

*To advance the profession of pharmacy, enabling our members to provide optimal care to those they serve.*

## **President's Letter**

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Welcome to the winter journal!

The journal committee has prepared outstanding information, articles, and continuing education about the importance of women's health.

We're so busy behind the scenes preparing for our upcoming events in March. We have two full day CE programs - March Madness, on March 12 at the College of St. Elizabeth in Morristown and Spring Fling on April 16 at the Holiday Inn in Cherry Hill. Both offer a variety of continuing education activities and law presentations. Online registration is open [enter [www.njpharmacists.org](http://www.njpharmacists.org), click the CE tab and select the CE calendar]. Please join us!

We have a strong line-up of regional programs, too, with great speakers, bursting with information, as well as have the opportunity to network with colleagues and friends. Members,

please have ready - proof of membership and your region if you sign up for a program at the door. Better yet, it's so much quicker & hassle-free for you and the NJPhA office staff if you register on-line!

Several members of our leadership team will be representing New Jersey as delegates during the annual APhA convention on March 4-8th in Baltimore; more information will follow about how that went in the summer journal!

You can also catch our +TonicRx events, held throughout the year if you prefer more socializing over education. I attended one of these events last year and it was memorable.

Professionally yours,  
Ruth Marietta, RPh, CCP  
President 2015-2016



### **It's Time to Consider a Leadership Role in NJPhA**

If involvement in your profession is your passion, consider taking a leadership role in shaping the future of pharmacy by becoming a candidate for NJPhA Second Vice President or Treasurer. Nominations are accepted from members in two ways:

- Send an email expressing your interest in either the Second VP position (1 yr. term) or Treasurer (2 yr. term)
- Nominate a member whom you believe is a good candidate for the Second VP or Treasurer position

Please include relevant information about candidate's qualifications, and add CANDIDATE in the subject line of your email to [ebarry@njpharma.org](mailto:ebarry@njpharma.org).

If you have any questions, please call the NJPhA office at 609-275-4246. The deadline is May 15, 2016.

## ***Message from the BOT Chairman***

Hello NJPhA! I can't believe an entire year has passed since my first message to you; wow, have we accomplished a lot!

I'd like to take a minute to reflect on the accomplishments of my leadership team last year, including the legislative impact in both New Jersey and the nation, the start of our social events under Tonic+, innovative regional and student programming and the incredible turn out for our 145th Annual Meeting and Convention at Harrah's Atlantic City - I don't know about you all but I had a blast!

As we move in to 2016, as the Chair of the Board, I have asked the Board to focus on increasing our non-dues revenue through innovative partnerships, educational events and certificate programs. I will also support Ruth and the Committee Chairs in their efforts, especially around Legislative Advocacy and Membership.

Our Advocacy Team actively works with APhA – American Pharmacists Association, NCPA – National Community Pharmacists

Association and others to protect our best interests and promote grassroots federal advocacy on key issues. It is not enough to influence law changes only. We must also influence regulations in order to affect change – our team works with the NJ Board of Pharmacy, Board of Medical Examiners, Drug Utilization Review Board, Health Information Technology Committee, NABP – National Association of Boards of Pharmacy, and the Center for Medicare & Medicaid Services (CMS) to make positive changes for pharmacists in every day practice.

Remember, NJPhA is the only organization that lobbies on behalf of ALL pharmacists in the State of New Jersey – spread the word, tell your friends, stay connected, and pave a path forward for our profession!

Hope to see you all at the next event!

Warm Regards,

Moriah Weissman, PharmD, CCP

## ***From The Editor's Desk...***

Dear Colleagues,

Hoping that everyone has made it a productive winter, despite the blizzard we experienced! I am looking forward to the signs of spring, with grass and the early blooming flowers.

The *NJ Journal of Pharmacy* – the official peer-reviewed journal of the NJ Pharmacists Association is pleased to provide this issue that is dedicated to women's health. This issue will focus on the recent changes to labeling concerning pregnancy and lactation, an overview on the human papilloma virus, the use of Raltegravir in HIV-Infected pregnant women and the novel new drug, Flibanserin, used for the treatment of hypoactive sexual desire disorder indicated for pre-menopausal women. You can earn continuing education by completing and submitting the Ohio CE which focuses on four new marketed medications - Cosentyx®, Ibrance®, Lenvima®, and Unituxin®. We also offer a free CE which reviews a current clinical and legal overview of oral emergency contra-

ception. Our pharmacy spotlight is a commentary on women in pharmacy.

Thank you for continuing to support the *NJ Journal of Pharmacy* and as always, please consider becoming active in the development of the *NJ Journal of Pharmacy*, through either submission of an article, or becoming a peer-reviewer. If interested please reach out to me, Elise Barry, or one of the NJPhA officers. You may email ideas and submissions or concerns to marcella.r.brown@gmail.com. I can help you with a topic consideration for the journal.

Looking forward to warmer weather!

Marcella R. Brown BSPharm, MS, PharmD, MPH, CGP, BCACP  
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### **Writers and Researchers:**

**Submit an article or a CE home study for a future issue of the  
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**Spring 2016 - Social Aspects of Pharmacy** - Author Deadline: April 15, 2016

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**Fall 2016 - Infectious and Respiratory Diseases** - Author Deadline: November 1, 2016

To submit an article or home study, request submission guidelines or for more information, please email the editor at the address above.

# Addyi™ (Flibanserin) for the treatment of hypoactive sexual desire disorder (HSDD)

By: Abdilahi Mohamed, Pharm.D., Ayse Elif Özdener, Pharm.D.  
and Małgorzata Slugocki, Pharm.D.

## Introduction:

According to the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision (DSM-IV-TR), hypoactive sexual desire disorder (HSDD) is defined as a persistent or recurrent insufficiency or absence of sexual fantasies and desire for sexual activity caused by distress or interpersonal difficulty that is not associated with other psychiatric disorders (e.g. depression), substance abuse (e.g. illicit drug), prescription and non-prescription medications or other medical conditions.<sup>1-4</sup> The new DSM-5 edition redefines the HSDD diagnosis as 'Female Sexual Interest/Arousal Disorder' which links together the desire and arousal into one disorder because desire and arousal are difficult to separate. To meet this new definition, the patient's symptoms must be persistent for at least 6 months.<sup>5</sup> Historically, most clinicians focused on male sexual dysfunction, and there was little known about female sexual dysfunction. Until recently, there was no standardized method for diagnosing women with sexual disorder. It is crucial to understand that HSDD is a multifaceted condition. In order to properly diagnose HSDD, clinicians need to understand the underlying causes. There are many factors that can cause women to develop low sexual desire. The underlying causes of female sexual problems may be due to biological, hormonal, medicinal or psychological factors. For instance, biological factors such as aging can cause low libido. The fluctuation of neuroendocrine hormone levels such as estrogen and androgen is also a known cause of low sexual desire. Psychological conditions including depression and anxiety may interfere with sexual desire. It is also very important to assess whether the disorder is due to substance abuse (e.g., alcohol, marijuana and cocaine) or other medications (e.g., antihypertensives, antipsychotics and antidepressants).<sup>3,4,6-8</sup>

An emerging hypothesis suggests that the etiology of female sexual dysfunction may encompass the reduced excitatory or increased inhibitory neurotransmitter activity in the central nervous system (CNS). Dopamine and norepinephrine are the two important excitatory neurotransmitters that play a leading role of female sexual arousal and orgasm, whereas serotonin is the main inhibitory neurotransmitter during sexual activity. The imbalance of these neurotransmitters is recognized to be the cause of HSDD.<sup>1,3,4,6,7,9</sup>

HSDD is divided into four categories depending on the duration and underlying cause(s) of the sexual dysfunction. These four categories include lifelong, acquired, generalized and situational. Women who fall under the lifelong HSDD category have never experienced healthy sex or orgasm whereas the acquired HSDD type is usually developed after women have had healthy sex life or orgasm. The context of sex disorder is further sub-classified as the generalized HSDD type, that is present all the time regardless of partner, stimulation or situation, or the situational HSDD is limited to certain conditions.<sup>2</sup> HSDD occurs globally, but its prevalence varies worldwide depending on the population type, culture, belief

system, age group studied, and relationship status. Among the US population, nearly 8.3% of women are suffering from HSDD.<sup>10</sup>

On August 18, 2015, the US Food and Drug Administration (FDA) approved Addyi™ (flibanserin) by Sprout Pharmaceuticals as the very first non-hormonal drug that is indicated for treatment of premenopausal women with acquired, generalized HSDD.<sup>1</sup> The approval for flibanserin came after two previous rejections by the FDA. In June 2010, the FDA rejected the first application of flibanserin filed by Boehringer Ingelheim because the clinical trial data concluded that flibanserin was not superior to placebo for the treatment of HSDD. In June 2013, the FDA rejected the second application of flibanserin, this time reapplied by Sprout Pharmaceuticals, because the data concluded that the risk of somnolence, dizziness, nausea, and fatigue outweighed the benefits of the drug.<sup>11</sup> The approval of flibanserin has received a lot of publicity. Flibanserin has often been called "women's Viagra". It is important to note that while both medications address sexual dysfunction, Viagra® (sildenafil) improves performance whereas flibanserin is intended to increase sexual desire. Furthermore, Viagra is meant to be taken as needed whereas flibanserin has to be taken daily to show benefit. This review article is intended to focus on flibanserin's mechanism of action, pharmacokinetics, clinical efficacy and safety data, and its place in therapy for women suffering from HSDD.

## Pharmacology:

The actual mechanism of action of flibanserin is not known, but the drug directly binds to postsynaptic selective serotonin reuptake inhibitors (SSRIs) receptors. Flibanserin exerts two different effects on SSRIs receptors; it acts both as a 5-hydroxytryptamine (5-HT<sub>1A</sub>) receptor agonist, as well as 5-HT<sub>2A</sub> receptor antagonist in the prefrontal cortex. Furthermore, it also acts as a moderate antagonist for 5-HT<sub>2B</sub>, 5-HT<sub>2C</sub> and dopamine (D<sub>4</sub>) receptors thus increasing the level of dopamine and norepinephrine while decreasing the activity of serotonin activity in the brain.<sup>1,3,7,9,12</sup> Like other SSRIs, flibanserin has some antidepressant properties. However, during the investigational trials, it was discovered to be ineffective for the treatment of Major Depressive Disorder (MDD). Nevertheless, it was found to improve sexual desire in women, who were suffering from sexual dysfunction due to MDD and, consequently, the pharmaceutical company shifted their investigation to explore further the potential benefits of flibanserin for the treatment of HSDD.<sup>4,6</sup>

## Pharmacokinetics:

Flibanserin is available as a 100mg tablet that is orally administered once daily. It is usually dosed at bedtime in order to lessen the danger of common adverse effects such as, hypotension, syncope, and accidental injury related to CNS depression (e.g. dizziness, somnolence, sedation). Bioavailability of flibanserin is 33%. However, when taken with food, the extent of absorption is increased and the rate of absorption is delayed. Nearly 98% of flibanserin is bound to plasma protein, particularly albumin. The

mean half-life of flibanserin is about 11 hours and it takes 3 days to achieve steady state. It takes 8 weeks for the drug to show benefit.<sup>1</sup> Flibanserin is metabolized by hepatic cytochrome P450 (CYP450) enzymes, primarily CYP3A4, but also to a lesser extent by CYP2C19. Consequently, the drugs that induce CYP3A4 will considerably reduce the level of flibanserin concentration, whereas, drugs that inhibit this enzyme can significantly increase the plasma concentration. Moreover, concurrent use with alcohol will also increase CNS depression. Therefore, flibanserin is contraindicated with alcohol and moderate/strong CYP3A4 inhibitors. Flibanserin is known to inhibit P-glycoprotein (P-gp) transporters. Therefore, drugs that are substrates for P-gp such as digoxin should be closely monitored for possible toxicity. Patients with hepatic impairment should avoid the use of this medication. Conversely, patients with renal impairment do not need dose adjustment. Majority of flibanserin is eliminated in the feces (51%) while the remainder is excreted in urine (44%).<sup>1</sup>

### Clinical Efficacy

Sexual desire is a challenging parameter to measure as it involves self-assessment of a multifactorial experience. Despite this challenge, a number of randomized multicenter Phase III trials have investigated improvement in sexual function in patients treated with flibanserin, using endpoints such as number of satisfying sexual events (SSE), sexual desire score (eDiary), and total score on the Female Sexual Function Index (FSFI), as well as Female Sexual Distress Scale-Revised (FSDS-R).<sup>3,4,6</sup> The approval of flibanserin was based on the results of three pivotal trials. They were randomized, double blind, placebo-controlled 24-week studies: VIOLET, DAISY, and BEGONIA. All of them were conducted in North America. Collectively, the trials included 3,658 premenopausal women with HSDD. All three pivotal trials involved the dosage regimen ultimately approved for treatment (100mg daily at bedtime).<sup>3,4,6</sup>

The VIOLET trial compared flibanserin 50mg daily at bedtime and 100mg daily at bedtime with placebo.<sup>6</sup> The DAISY trial included three treatment arms: flibanserin 25mg twice daily, flibanserin 50 mg once daily at bedtime for 2 weeks followed by 50mg twice daily, and flibanserin 50mg once daily at bedtime for 2 weeks followed by 100mg once daily at bedtime.<sup>4</sup> Both trials demonstrated a statistically significant improvement in co-primary endpoints (SSE score and eDiary score) in the flibanserin 100mg daily at bedtime treatment arm.<sup>4,6</sup> In the VIOLET trial, the mean (standard error [SE]) change from baseline in SSE was 0.8 (0.20) in the placebo group, 1.4 (0.21) in the flibanserin 50mg daily at bedtime group ( $P < 0.05$  vs. placebo), and 1.6 (0.23) in the flibanserin 100mg daily at bedtime group ( $P < 0.01$  vs. placebo). The mean (SE) changes from baseline in eDiary were 6.9 (0.9) in the placebo arm, 8.2 (0.9) for flibanserin 50mg daily at bedtime arm ( $P = 0.26$  vs. placebo), and 9.1 (1.0) in the flibanserin 100mg daily at bedtime arm ( $P = 0.07$  vs. placebo).<sup>6</sup>

In the DAISY trial, the mean (standard error [SE]) changes from baseline in SSE were 1.1 (0.2) in the placebo group, 1.4 (0.2) in the flibanserin 25 mg twice daily group ( $P = 0.29$  vs. placebo), 1.4 (0.2) in the 50 mg twice daily group ( $P = 0.20$  vs. placebo), and 1.9 (0.3) in the 100 mg daily at bedtime group ( $P = 0.01$  vs. placebo). The mean (SE) changes from baseline to end of study in the

monthly eDiary sexual desire score were 6.8 (0.8) in the placebo arm, 7.9 (0.8) in the flibanserin 25 mg twice daily arm ( $P = 0.28$  vs. placebo), 8.8 (0.8) in the 50 mg twice daily arm ( $P = 0.06$  vs. placebo), and 8.5 (0.8) in the 100 mg daily at bedtime arm ( $P = 0.12$  vs. placebo).<sup>4</sup>

The BEGONIA study evaluated the efficacy of a 24-week treatment with flibanserin 100 mg daily at bedtime versus placebo. The change in adjusted (least squares) mean (standard error [SE]) FSFI score from baseline was 1.0 (0.1) with flibanserin and 0.7 (0.1) with placebo ( $P = 0.001$ ). The mean (SE) standardized SSE increased by 2.5 (4.6) with flibanserin and 1.5 (4.5) with placebo ( $P = 0.001$ ).<sup>3</sup>

The SNOWDROP trial was a non-pivotal 24-week randomized, double blind, placebo-controlled trial that included postmenopausal women who received either flibanserin 100mg daily at bedtime or placebo. The primary endpoints included change in baseline SSE score as well as FSFI score. The mean (SE) change from baseline in SSEs was increased by [1(0.1),  $P=0.004$ ] for flibanserin 100mg daily at bedtime versus 0.6(0.1) in the placebo group. The mean change from baseline in the FSFI score was improved by 0.7(0.1) in the flibanserin arm versus 0.4(0.1) with placebo ( $P < 0.001$ ).<sup>7</sup>

The results of these trials demonstrated a statistically significant difference between flibanserin 100 mg daily at bedtime as compared to placebo in premenopausal women with HSDD. Furthermore the results of SNOWDROP trial showed promising data in postmenopausal women diagnosed with HSDD.

### Safety and tolerability

The most common adverse effects reported in the pivotal trials (DAISY, VIOLET, and BEGONIA) were somnolence, dizziness, headache, nausea, insomnia, and fatigue.<sup>3,4,6</sup> Subjects in the VIOLET trial also reported adverse effects such as nasopharyngitis, upper respiratory tract infections, and sinusitis. Most of the subjects experiencing these adverse effects categorized them to be mild to moderate in severity.<sup>6</sup> Serious adverse effects were rare in all the clinical trials and all the adverse effects categorized as severe were deemed unrelated to the study drug by the investigators.<sup>3,4,6</sup> In all of the clinical trials, the rate of discontinuation was greater in the study drug arm compared to the placebo.<sup>3,4,6</sup> Two subjects (one in the placebo arm and one in the flibanserin arm) in the BEGONIA trial reported suicide ideation, but investigators did not consider this to be related to the study drug.<sup>3</sup>

The SNOWDROP and SUNFLOWER studies were non-pivotal trials.<sup>7,13</sup> It is important to note that in the SUNFLOWER trial, investigators looked at safety parameters as its primary endpoint.<sup>13</sup> Most adverse events in the SNOWDROP and SUNFLOWER trials were described as mild to moderate and similar to those in the pivotal trials.<sup>7,13</sup> The most common adverse events reported as severe in the SUNFLOWER trial were somnolence and influenza.<sup>13</sup> Like the VIOLET trial, subjects in the SUNFLOWER study also reported adverse events such as nasopharyngitis, upper respiratory tract infections, and sinusitis, all of which were deemed unrelated to the study drug by the investigators. There was one subject in the SUNFLOWER trial that reported suicide ideation, which was considered unrelated to flibanserin use.<sup>13</sup>

## **Conclusion:**

Since the approval of Viagra® (sildenafil) for male erectile dysfunction, many pharmaceutical companies shifted their research to discover an equivalent female agent. Although HSDD is a major problem for women of all ages, flibanserin is a treatment option for premenopausal women only.<sup>1</sup> While the SNOWDROP trial showed promising results in post-menopausal women, flibanserin is not yet indicated in this population or in men.<sup>7</sup> Based on the safety data reported in clinical trials, dizziness, somnolence, nausea, and headache seem to be the most common adverse events seen with flibanserin therapy. Flibanserin was approved with a Black Box Warning for risk of hypotension and syncope in patients who drink alcohol, use moderate-strong CYP3A4 inhibitors concomitantly, or have liver impairment. Therefore, flibanserin is contraindicated in these settings. Flibanserin is also under the risk evaluation and mitigation strategy (REMS) program.<sup>1</sup> There are several aspects of flibanserin therapy that have yet to be explored: duration of therapy, the use in elderly patients, and use in women who are in homosexual relationships. The true efficacy and safety of this medication will be better understood once it becomes more widely used for this disorder. In the meantime, patients need to be educated on abstinence from alcohol and the importance of adherence to the regimen for at least eight weeks to experience full benefit.

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<sup>1</sup>Addyi™ (flibanserin) [package insert]. Sprout Pharmaceuticals, Inc; Raleigh, NC: 2015.

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# Changes for the Better: New Pregnancy and Lactation Labeling Rules

By: Anita Kachappilly, Pharm.D. Candidate and Jane Park

## Abstract:

One of the biggest concerns that females of childbearing age bring to her healthcare provider is the safety of a drug before, during, and after pregnancy. Currently, drugs are categorized into merely 5 different categories (A, B, C, D, X) in which –much like a grading system used in academics – “A” is considered good, or in this case safe, and “X” is an absolute no. Although this system appears to be clear and concise, questions and concerns arise when dealing with medications that fall in between the A and the X. What about those drugs that are not an absolute ‘yes or no’, ‘black or white’? Often times we see the phrase “when benefit exceeds the risk,” which can be a vague and rather unhelpful answer for a pregnant woman, especially when she is trying to make an informed decision for both her and the unborn child. In order to facilitate this decision-making process, a new structure in the drug labeling has been proposed. This new labeling provides, in many different subunits, an extensive explanation on a drug’s effect and will hopefully serve as a useful guidance for all healthcare professionals.

According to the U.S. Food and Drug Administration (FDA), there are over 6 million pregnancies in the United States every year and on average, women will typically take 3 to 5 prescription medications during their pregnancies.<sup>1</sup> This may be due to chronic medical conditions starting prior to or new conditions developed during pregnancy. That being the case, it is extremely important to address the possibility of side effects and teratogenic potential of medications in a way that is clear for health care professionals to make an informed prescribing decision. In 1979, under the Food, Drug, and Cosmetic Act, the FDA began issuing rules for labeling on the use of the medication during pregnancy, labor and delivery, and by nursing mothers. In addition, these regulations created pregnancy categories – A, B, C, D, and X – in which, the letter assigned to each drug reflects its level of teratogenic risk.<sup>2</sup> Currently, this information can be easily obtained through the manufacturer’s package insert or books like *Drugs in Pregnancy and Lactation* (Briggs & Freeman, 2011).

This classification system, however, has its flaws. As explained by Sandra Kweder M.D., Deputy Director of the Office of New Drugs, “The letter category system was overly simplistic and was misinterpreted as a grading system, which gave an over-simplified view of the product risk.”<sup>1</sup> The pregnancy categories became a quick reference and did not effectively help health care providers weigh the risks and benefits of a medication, especially if a patient has limited options. With an array of data on fetal risk with drugs, compartmentalizing the information into 1 of 5 categories may lead to misunderstandings on proper use. It can be gathered that Category A and B medications most likely will cause no fetal harm, and Category X medications should be avoided in pregnancy. Confusion can lie, however, within Category C and D medications where benefits may outweigh the risks, but to what degree? Also, according to Lynn Martinez, a senior teratogen information

specialist, many drugs may be categorized as C, D, or X agents to protect the manufacturing companies from the possibilities of birth defect- related lawsuits.<sup>5</sup> This is a cause for misinformation on medications that may actually help a patient. Fortunately, the FDA recognized the shortcomings to this format and has finalized a new rule for pregnancy and lactation labeling.

The final rule for Pregnancy and Lactation labeling became effective as of June 30, 2015 and contains changes to the previous guidelines. The largest revisions were the removal of the pregnancy letter categories and changes in the subsections within “Use in Specific Populations.” The labeling format now consists of 3 new or modified subsections titled *Pregnancy*, *Lactation*, and *Females and Males of Reproductive Potential*. The purpose of these new sections is to provide detailed information in an organized and consistent matter so that it can be easily located and assessed by health care professionals. The first 2 sections must be included in the labeling and require a summary of the risks of using the drug, and if possible, a discussion of the supporting data and other relevant information that may be helpful. The section about reproductive potential is only needed if data regarding this topic are available.<sup>2</sup> Hopefully these improvements will help health care providers when making informed decisions about prescribing and counseling, especially when a mother and/or child may be at risk.

The new Pregnancy subsection (8.1) is a combination of the former Pregnancy subsection and the Labor and Delivery subsection. It requires a Risk Summary subheading, which details the possible adverse outcomes of the drug, if any, when used during pregnancy in regard to the mother, fetus, or infant. The summary is based on pertinent animal data, human data, and/or the pharmacologic mechanism of the drug. Other subheadings that should be included, if applicable, are Clinical Considerations, Data, and Pregnancy Exposure Registry. The Clinical Considerations component provides relevant information to help with prescribing and counseling, and the Data component describes the scientific data that support the information in the Pregnancy subsection. A great addition to the label is the Pregnancy Exposure Registry subheading. A pregnancy exposure registry is a study that collects information on pregnant women taking prescription drugs or vaccines.<sup>3</sup> The subheading will state if a scientifically acceptable registry is available along with information on how to enroll. Previously, registries were only included in the labeling if they were available; however, now the purpose of this new section is to increase participation in these registries and enhance data collection of the effects of a drug. The registry information is also placed first in the Pregnancy subsection in order to better inform a prescriber about the availability of the program and gain a greater amount of clinical data that can, in turn, improve future labeling.

The next subsection is Lactation (8.2), which replaces the former Nursing Mothers subsection and describes the risks of using

the drug when breastfeeding. Like the Pregnancy subsection, this subsection also requires a Risk Summary and Clinical Considerations and Data subheading, if applicable. The Risk Summary is slightly different in this case, in that it explains information on the presence of the drug in human milk, the effects of the drug on a breastfed child, and the effects on milk production. If the drug has been detected in human milk, it must be mentioned at what concentration relative to the dose taken by the mother. Other detailed information that must be included is an estimate of the amount of drug that could be consumed daily by the child and an estimate of the percentage of maternal dose excreted into milk. In terms of the child, information must be provided on how he or she may be affected from exposure through breast milk, as well as pharmacokinetics data based on age. The Clinical Considerations section contains more information that may help with prescribing and counseling, such as minimizing exposure to the child and monitoring for adverse effects.

The final subsection, Females and Males of Reproductive Potential (8.3), is new and contains information that did not have consistent placement before, previously making it difficult for health care professionals to locate. It gives information on whether a pregnancy test or contraception is required before, during, or after

drug use. It also includes data about drug related effects on fertility. The ease of access within the labeling should help with counseling patients, especially those of reproductive age.<sup>2</sup>

Any drug or biological product application submitted on or after effective date of June 30, 2015 is subject to following the new labeling rules. Implementation of the rule for other application holders depends on the status of the application or time of approval. Any applications approved on or after June 30, 2001 are subject to follow the "Physician Labeling Rule" of 2006. These products are given a phase-in implementation plan based on when their application was approved. For example, a drug that was approved between June 30, 2002 and June 29, 2005 has five years after the effective date of the pregnancy final rule to submit the new content for FDA approval. A drug that was approved between June 30, 2001 and June 29, 2009, however, has 3 years from the effective date. Applications approved prior to June 30, 2001 also have 3 years to remove the pregnancy category and submit updated labeling information.<sup>2</sup> This final rule will only affect prescription medications and biological products, not over the counter medications.<sup>4</sup>

The purpose of prescription drug labeling is to effectively communicate important information on the use of a drug to healthcare providers. The new revisions on pregnancy and lactation labeling are great steps taken to efficiently achieve that objective. Hopefully, this format will help prescribers and pharmacists make more informed decisions for patients within these populations and lead to safer drug use.

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## **Oral Emergency Contraception – Clinical and Law Overview for the Pharmacist**

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### **Learning Objectives:**

**After participating in this activity, the participant shall be able to:**

#### **Pharmacist:**

1. Define Emergency Contraception.
2. Describe the different types of Emergency contraceptives that are available.
3. Explains the regulations surrounding the dispensing of emergency contraception.

**Author disclosures: Neither author has a conflict of interest in relation to this activity**

**CEU Hours: 1 contact hour of continuing education credit (0.1 CEU)**

**Activity type: Knowledge-based**

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### **INTRODUCTION**

Emergency contraception (EC) is defined by the World Health Organization (WHO) as contraception that, when used within the first few days after sexual intercourse, can prevent pregnancy. WHO intends EC to be utilized by women of childbearing age after unprotected sexual intercourse, when contraception fails, is forgotten, or is not used properly, after rape, and after coerced sex. Currently, there are two types of EC: oral tablets (commonly referred to as "morning after pills") and intra-uterine devices (IUDs).<sup>1</sup> These are summarized in Table 1. This article will focus on oral EC in the pharmacist's practice.

Since EC was first FDA approved in the United States in 1999, the CDC reports that up to 11 % of females had used oral EC at least once between 2006 and 2010. Of these females, 42% had used oral EC two or more times. Approximately half of the users (43% to 60% depending on educational level and race) report using EC because of unprotected sex.<sup>2</sup>

There are three methods of oral EC used in the US:

1. combined hormone pill
2. single hormone pill
3. ulipristal<sup>3</sup>

Table 1 – Comparison of EC available in the United States

EC type	drug class(es)	medicinal compound	common Brand names	dosage and administration	legalities for dispensing	AWP4
combined hormone pill (aka Yuzpe Method <sup>5</sup> using oral contraceptives on the market)	estrogen + progestin	equivalent to ethinyl estradiol 100 mcg + 500 mcg progestin	multiple OC on the market can be used	# of tablets depends on the brand. Range is 2 to 6 tablets per dose. <sup>6</sup>	Rx only	varies. Must purchase monthly OC pack
single hormone pill	progestin-only	levonorgestrel	Plan B	0.75 mg po x 2 doses, 12 hours apart	OTC	\$37
			Plan B One Step	1.5 mg po x 1 dose		\$42
ulipristal	progesterone agonist/antagonist	ulipristal acetate	Ella	30 mg po x 1 dose	Rx only	\$43
IUD	device	intrauterine copper device	Paragard		Inserted by physician	\$754 + MD office visit <sup>3</sup>

EC = emergency contraception

po = by mouth

MD = physician or healthcare provider

OC = oral contraception

Rx = prescription

### COMBINED HORMONE EC

Oral EC dates back to the 1970's when the Yuzpe Method<sup>5</sup> was first introduced. This method, named for the author that first described using oral contraceptives (OC) after sex to prevent pregnancy, entails the woman taking 2 doses of commercially available birth control pills that contain the equivalent of 100 mcg estrogen and 500 mcg progestin.<sup>7</sup> The first of the doses is to be taken within 72 hours of sex to reduce the risk of pregnancy by at least 75%. The second dose is taken 12 hours after the first dose.<sup>3</sup>

The Yuzpe Method prevents pregnancy by inhibiting or delaying ovulation. Other proposed mechanisms of action include interfering with functioning of the corpus luteum, dysfunctional ovulation, and cervical mucus thickening that traps sperm.<sup>8</sup>

Many birth control pills that contain ethinyl estradiol + norgestrel or ethinyl estradiol + levonorgestrel in the US are FDA-approved for use as oral EC; and the FDA stated in 1997 that the use of birth control pills in the Yuzpe Method is safe and effective.<sup>9</sup> The number of tablets to be taken depends on the product and on the color of the pill in the pack, as different products contain varying amounts and types of estrogen and progestin components. Dosing examples that are approved by the FDA are included in Table 2.

Table 2: Equivalent doses of estrogen + progestin components of OC per FDA<sup>10</sup>

Amount of estrogen + progestin per pill	Number of pills needed to equal 100 mcg estrogen + 500 mcg progestin
50 mcg ethinyl estradiol + 500mcg norgestrel	2 tablets
20 mcg ethinyl estradiol + 100 mcg levonorgestrel	5 tablets
30 mcg ethinyl estradiol + 150 mcg levonorgestrel	4 tablets

Since not all commercially available products that came to market after the FDA ruling in 1997 have these fixed ratios of estrogen + progestin combinations, approximations in amounts of estrogen + progestin are acceptable.<sup>11</sup> Table 3 lists common OC that are used for EC and the number of tablets to be utilized per dose. A comprehensive list can be found on the Planned Parenthood website at [https://www.plannedparenthood.org/files/5713/9611/6188/Emergency\\_Contraception\\_History\\_and\\_Access.pdf](https://www.plannedparenthood.org/files/5713/9611/6188/Emergency_Contraception_History_and_Access.pdf).

Table 3: Yuzpe method doses for common OC for use as EC

oral contraceptive	color of pill in pack	content of one pill	number of pills per dose
Alesse® <sup>12</sup>	pink [active] pills	20 mcg ethinyl estradiol + 100 mcg levonorgestrel	5 tablets
Nordette® <sup>13</sup>	light-orange [active] pills	30 mcg ethinyl estradiol + 150 mcg levonorgestrel	4 tablets
Lo/Ovral® <sup>6,9,11</sup>	white [active] pills	30 mcg ethinyl estradiol + 300 norgestrel	4 tablets
Triphasil® <sup>11</sup>	light yellow [phase 3] pills	30 mcg ethinyl estradiol + 125 mcg levonorgestrel	4 tablets

Nausea can occur in up to 50% of women, and vomiting in up to 20 %. Vomiting within one hour of the dose warrants repeating the same dose.<sup>7</sup> Physicians may also wish to prescribe antiemetics for use prior to dosing to prevent nausea and vomiting.<sup>3</sup>

#### SINGLE HORMONE EC

Single hormone EC consists of the progestin levonorgestrel in a total dose of 1.5 mg. This can be taken as follows:

- a single dose of one 1.5 mg tablet
- a single dose of two 0.75 mg tablets taken at the same time
- two doses of 0.75 mg tablets, taken 12 hours apart.<sup>3</sup>

The selected regimen should be initiated as soon as possible within 72 hours of intercourse, resulting in up to 79% effectiveness. Efficacy is the same regardless of the regimen, and is greater the closer it is taken to intercourse, and begins to decline as time passes.<sup>3,14</sup> The dose should be repeated if vomiting occurs within two hours of the dose, although vomiting is not a common side effect.<sup>14</sup>

Commercially available products of levonorgestrel for EC are available as brand name products and generic products by various manufacturers. Examples of common manufacturers and brand names of the 1.5 mg tablet include: Plan B One-Step® (Teva Women's Health), EContra EZ® (Afaxys), Fallback Solo® (Lupin Pharmaceuticals, Inc.), My Way® (Gavis Pharmaceuticals), and others.<sup>15</sup>

The 0.75 mg tablets originally available as Plan B® are discontinued by the manufacturer. However, the medication may still be available from some generic manufacturers and wholesalers under different trade names.<sup>15</sup>

Levonorgestrel prevents ovulation and alters the transport of the sperm and egg to prevent fertilization. It may also alter the endometrium to prevent implantation. Levonorgestrel will not terminate a pregnancy if the fertilized egg is already implanted.<sup>14</sup>

In addition to vomiting, heavy menstrual bleeding may occur in up to 31% of patients. Other side effects with an incidence of at least 10% include nausea, lower abdominal pain, fatigue, dizziness, and headache. Patients may also experience breast tenderness and a late period.<sup>14</sup>

Plan B® was approved by the FDA for prescription use only in 1999 for women of all ages to use as emergency contraception.<sup>16</sup> In 2003, the application for Plan B® to switch from prescription only to over-the-counter (OTC) was submitted, however the request was rejected by the FDA due to lack of data in women under the age of 16.<sup>17</sup> The main concerns that surfaced were whether Plan B® can remain as both prescription and OTC depending on age, whether prescription and OTC versions of the same drug can be marketed in the same package, and whether an age restriction can be enforced.

It was not until 2006 that Plan B® was approved by the FDA as an OTC form of EC for women ages 18 years and older.<sup>16</sup> Nevertheless, women 17 years of age and younger still needed a doctor's prescription. As a result, Plan B® was mandated to be stocked behind the pharmacy counter as a method to enforce this age restriction.<sup>18</sup> Three years later, a federal judge ordered that the FDA must make Plan B® available OTC to women as young as 17 years of age after examining a previous court ruling and citing viola-

tions. Specifically, agency officials were delaying action on this petition, violating policies, and providing improper communication with White House officials.<sup>18</sup>

Therefore, in April 2009 the FDA announced that Plan B® can be sold OTC for women and men 17 years of age and older, though the manufacturer, Duramed Pharmaceuticals, did not receive approval for such availability until July of that year.<sup>16</sup> At this time, Duramed Pharmaceuticals began manufacturing Plan B One-Step®, the one-dose version of Plan B®, for women ages 17 years and older and prescription availability of Plan B One-Step® for women younger than 17. That same summer, a generic version, under the trade name Next Choice®, was also approved by prescription for women 17 years of age and under.<sup>16</sup> Two years later, two additional one-pill products (Next Choice One Dose® and My Way®) were approved.<sup>19</sup>

In 2011, another pharmaceutical company (Teva) submitted data to the FDA on the actual use and label-comprehension of females <18 years of age.<sup>17</sup> Later that year, the FDA approved Plan B® with no age restriction; however it was overruled by the Secretary of Health and Human Services.<sup>17</sup> The following year in 2012, Teva revised their application for Plan B One-Step® to become available for women 15 years and older without a prescription.<sup>19</sup> This application became approved in April 2013, though all age restriction was removed two months later.<sup>17</sup> In February 2014, the FDA approved generic one-pill emergency contraception products for unrestricted sale on the shelf.<sup>17</sup> Then once Teva's exclusivity expires in August 2016, all one-pill emergency contraceptives will be able to be sold on the shelf.<sup>19</sup>

#### **ULIPRISTAL TABLETS**

Ulipristal 30 mg tablets have been on the market in the U.S. since 2010, under the trade name Ella® (Afaxys, Inc.). Ulipristal is a synthetic progesterone receptor antagonist and partial agonist that most likely prevents pregnancy by inhibiting or delaying ovulation. It may also inhibit implantation of the fertilized egg by affecting the endometrium. One tablet of ulipristal is to be taken as soon as possible, within 120 hours of sexual intercourse. If the patient vomits within three hours of the tablet, the dose should be repeated.<sup>3,20</sup>

Ulipristal is reported to have superior efficacy in preventing pregnancy when compared to levonorgestrel. In clinical trials, ulipristal resulted in a 42% lower pregnancy rate than levonorgestrel.<sup>21</sup>

The most commonly reported side effects include headache (up to 19% incidence), nausea (up to 13% incidence), abdominal pain (up to 15% incidence), dysmenorrhea (up to 13% incidence), fatigue and dizziness (up to 6% incidence each).<sup>20</sup>

#### **NEW JERSEY SPECIFIC LAW**

Pertinent dates in EC history are outlined in Figure 1. In addition to federal laws, there are two laws in NJ that affect the utilization of EC. Healthcare facilities that provide medical care to victims of sexual assault are required to provide EC upon request. These facilities are also required to provide information about EC and to train their personnel to provide care and information regarding EC to the victims.<sup>22</sup>

Additionally, NJ pharmacy law indicates that the pharmacy must not refuse to fill a prescription because of the practitioner's "sincerely held moral, philosophical or religious beliefs." If the pharmacy does not have the prescription medication in stock, it must offer to either order the drug or transfer the prescription to an accessible pharmacy that has the medication in stock, whichever the patient chooses.<sup>23</sup>

#### **CONCLUSION**

The pharmacist's role in EC required the pharmacist to be knowledgeable in the pharmacology, administration, and counselling points, in addition to understanding and complying with federal and state laws regarding EC.

#### **ACKNOWLEDGEMENT**

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# Clinical Overview of Human Papillomavirus (HPV) Vaccines

By Oishi Rahman, Pharm.D. Candidate 2016, Brian Tong, Pharm.D. Candidate 2016  
and Kimberly Erin Ng, Pharm.D., BCPS\*

Human papillomavirus (HPV) is one of the most common sexually transmitted infection in the United States, with an estimated 79 million Americans currently infected.<sup>1</sup> Nearly all sexually active men and women become infected with at least one type of HPV in their lifetime.<sup>1,2</sup> Although 90% of HPV infections are asymptomatic and resolve spontaneously within two years, recurrent HPV infections can potentially lead to genital warts and cancer.<sup>3</sup> It is estimated that 360,000 people develop genital warts while over 11,000 women develop cervical cancer in the United States each year.<sup>1</sup> Of the more than 120 types of HPV identified, approximately 40 types have been found to infect the genital tract.<sup>2,3</sup>

HPV types are categorized based on their associated risk of causing cervical cancer. Low-risk HPV types include 6 and 11; an infection with these two types can result in low-grade cervical cell abnormalities, genital warts or laryngeal papillomas. High-risk HPV types include 16 and 18; an infection with these types may lead to the development of cervical cancer.<sup>2,4</sup> It is reported that type 16 is the cause of 50% of cervical cancers while types 16 and 18 together are the cause of 70% of cervical cancers.<sup>2</sup> Table 1 classifies HPV types based on their risk of cervical cancer, according to an international study of 1,918 women with cervical cancer and 1,928 control women.<sup>5</sup> In addition to cervical cancer, HPV can cause vulvar, vaginal, penile, anal and oropharyngeal cancer.<sup>1,2</sup> Vaccination can prevent infection with the most common types of HPV associated with cervical cancer risk, including types 6, 11, 16, 18, which are present in the quadrivalent HPV vaccine (qHPV) and 31, 33, 45, 52, and 58, which are present in the nine-valent vaccine in addition to the four types in the qHPV.<sup>5-7</sup>

Table 1. HPV Types and Cervical Cancer Risk<sup>5</sup>

Risk of Cervical Cancer	HPV Types
High-Risk	16*, 18*, 31*, 33*, 35*, 39, 45*, 51, 52*, 56, 58*, 59, 68, 73, 82
Probable-High Risk	26, 53, 66
Low-Risk	6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81, CP6180

\*Denotes the most common HPV types in patients with cervical cancer

## HPV Pathogenesis

HPV is a double-stranded deoxyribonucleic acid (DNA) virus of approximately 8000 base pairs.<sup>8,9</sup> Research has shown that HPV DNA is present in anogenital cancers and is necessary to immortalize malignant cells. The HPV oncogenes are also necessary to maintain the malignant state.<sup>8</sup> Among its oncogenes are two well-studied early (E) gene regions, E6 and E7, that disrupt important cell cycle proteins. The E6 oncoprotein binds to and degrades p53, preventing apoptosis of infected cells.<sup>9</sup> The E7 oncoprotein binds to the retinoblastoma protein and ultimately results in mutagenic events.<sup>8</sup> The cell-mediated immune response, especially of CD4+

T cells, plays a key role in preventing the progression of HPV infection. Protection against specific types of HPV occurs due to the presence of neutralizing antibodies present at the site of infection and persists as long as the concentration is sufficient.<sup>4</sup>

## Currently Available HPV Vaccines

The approval of the first HPV vaccine in 2006 was a vital stepping stone in the development of additional HPV vaccines and the prevention of HPV related conditions.<sup>2</sup> The L1 capsid proteins within the vaccine self-assemble into virus-like proteins (VLPs) when expressed by cells.<sup>4,10</sup> The VLPs contain the same antigenic determinants as the HPV virion; however, the VLPs do not have viral DNA and cannot cause infection.<sup>4</sup> Immunity of the host depends on the development of antibodies to antigenic determinants present on the viral capsids.<sup>4</sup>

Three HPV vaccines are currently available in the United States: Cervarix® (2vHPV vaccine), Gardasil® (qHPV vaccine), and Gardasil 9® (9vHPV vaccine).<sup>6, 7, 11</sup> Gardasil 9®, the most recent of these three vaccines to be approved by the FDA, provides protection against an additional five HPV types: 31, 33, 45, 52, and 58, in addition to HPV types 6, 11, 16 and 18.<sup>7</sup> These additional HPV types cause approximately 20% of cervical cancers and are not covered by the other two available HPV vaccines.<sup>12</sup> Table 2 summarizes the three FDA-approved HPV vaccines and their indications.

Table 2: Currently Available HPV Vaccines

Vaccine	HPV Types	Initial Approval	Indications
Gardasil® <sup>6</sup> (Merck)	Quadrivalent: <ul style="list-style-type: none"><li>• HPV-6</li><li>• HPV-11</li><li>• HPV-16</li><li>• HPV-18</li></ul>	2006	<b>Girls and Women Ages 9 through 26:</b> <ul style="list-style-type: none"><li>• Prevention of cervical, vulvar, vaginal and anal cancers caused by HPV 16 and 18</li><li>• Prevention of genital warts caused by HPV 6 and 11</li><li>• Prevention of CIN grades 2/3 and cervical AIS, CIN grade 1, VIN grades 2/3, VaIN grades 2/3, and AIN grades 1/2/3 caused by HPV 6, 11, 16, and 18</li></ul> <b>Boys and Men Ages 9 through 26:</b> <ul style="list-style-type: none"><li>• Prevention of anal cancer caused by HPV 16 and 18</li><li>• Prevention of genital warts caused by HPV 6 and 11</li><li>• Prevention of AIN grades 1/2/3 caused by HPV 6, 11, 16, and 18</li></ul>

Table 2 continued on next page

Vaccine	HPV Types	Initial Approval	Indications
<b>Cervarix®<sup>11</sup> (GlaxoSmithKline)</b>	Bivalent • HPV-16 • HPV-18	2009	<b>Girls and Women Ages 9 through 25:</b> • Prevention of cervical cancer • Prevention of CIN grade 2 or worse and AIS • Prevention of CIN grade 1 <b>Boys and Men:</b> • Not Indicated
<b>Gardasil-9®<sup>7</sup> (Merck)</b>	9-Valent: • HPV-6 • HPV-11 • HPV-16 • HPV-18 • HPV-31 • HPV-33 • HPV-45 • HPV-52 • HPV-58	2014	<b>Girls and Women Ages 9 through 26:</b> • Prevention of cervical, vulvar, vaginal, and anal cancer caused by HPV 16, 18, 31, 33, 45, 52, and 58 • Prevention of genital warts caused by HPV 6, 11 • Prevention of CIN grade 2/3 and AIS, CIN grade 1, VIN grades 2/3, VaIN grades 2/3, and AIN grades 1/2/3 caused by HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 <b>Boys Ages 9 through 26:</b> • Prevention of anal cancer caused by HPV 16, 18, 31, 33, 45, 52, and 58 • Prevention of genital warts caused by HPV 6 and 11 • Prevention of AIN grades 1/2/3 caused by HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58

**Abbreviations:** AIN-anal intraepithelial neoplasia, AIS-adenocarcinoma *in situ*, CIN-cervical intraepithelial neoplasia, VaIN-vaginal intraepithelial neoplasia, VIN-vulvar intraepithelial neoplasia

### Recommendations for HPV Vaccinations

The most recent Advisory Committee on Immunization Practices (ACIP) recommendations regarding the HPV vaccinations were made available in the Morbidity and Mortality Weekly Report on March 27, 2015. The ACIP updates incorporate evidence for the recommendation of the 9vHPV as one of the HPV vaccines for routine vaccination. Table 2 provides an overview of the current ACIP recommendations regarding HPV vaccine administration.<sup>10</sup> These new recommendations will be included in the immunization schedules that the ACIP will publish in February 2016.<sup>13</sup>

### Administration Schedules

All three vaccines are administered in a three-dose schedule (0.5 mL each). The second dose is administered one to two months after the first dose, and the third dose is administered six months after the first dose. Should the recommended administration schedule be interrupted, the vaccination series does not have to be re-initiated. If the vaccine previously administered is unknown, any of the three vaccines may be administered to continue or complete the series for females. Likewise, either the qHPV or 9vHPV may be administered to continue or complete the series for males.<sup>10</sup>

**Table 3: Current ACIP Recommendations for HPV Vaccinations<sup>10</sup>**

Women	Men
<b>Initiation Age:</b> 11 or 12 years; may initiate at age 9*	
<b>Age 13 through 26:</b>	<b>Age 13 through 21:</b>
<input type="checkbox"/> Women who have not previously received an HPV vaccination	<input type="checkbox"/> Men who have not previously received an HPV vaccination
<input type="checkbox"/> Women who have yet to complete the three-dose series (see “Administration Schedules”)	<input type="checkbox"/> Men who have yet to completed the three-dose series
	<b>Age 22 through 26:</b>
	<input type="checkbox"/> Men who have sex with men
	<input type="checkbox"/> Immunocompromised persons (i.e. HIV infection)
<b>Recommended vaccines:</b>	<b>Recommended vaccines:</b>
<input type="checkbox"/> 2vHPV	<input type="checkbox"/> qHPV
<input type="checkbox"/> qHPV	<input type="checkbox"/> 9vHPV
<input type="checkbox"/> 9vHPV	

\*For routine vaccination, ACIP recommends initiating the 3-dose series at age 11 or 12 years. The vaccination series can also be initiated at age 9 years. Children at age 9 years with history of sexual abuse or assault that have not initiated or completed the 3-dose series can be administered the vaccine. Vaccination is also recommended for females 13 to 26 years and men 13 to 21 years who have not previously received the vaccination or have not completed the 3-dose series. Vaccination is also recommended for men 22 to 26 years who have sex with men and for immunocompromised persons.

### Contraindications, Precautions, and Adverse Events

All three HPV vaccines are contraindicated in individuals with hypersensitivity reactions to any vaccine component. The 2vHPV should not be used in those with anaphylactic latex allergy because the tips of the prefilled syringes may contain natural rubber latex.<sup>10,11</sup> The qHPV and 9vHPV are contraindicated in individuals with a history of hypersensitivity to yeast because it is a vaccine component.<sup>6,7,10</sup>

As per manufacturer package inserts, syncope, sometimes associated with tonic-clonic movements and other seizure-like activity, has been reported after HPV vaccination. Therefore, a fifteen-minute observation period after vaccine administration is recommended. Syncope associated with tonic-clonic movements has been reported to be transient and responds to restoring cerebral perfusion by maintaining a supine or Trendelenburg position.<sup>6,7,9-11</sup>

HPV vaccines are not recommended for pregnant women. If a woman becomes pregnant after initiating the vaccination series, the remainder of the three-dose series should be delayed until after pregnancy. No intervention is required if HPV vaccine has been administered during pregnancy. There is a pregnancy registry for 9vHPV and any vaccine exposure during pregnancy may be reported to the corresponding manufacturer for 2vHPV and qHPV or the Vaccine Adverse Event Reporting System (VAERS). Adverse events after administration of any vaccine should also be reported to VAERS.<sup>10</sup>

The most common adverse events associated with all HPV vaccines are injection site reactions, which include pain (71% to 90%), swelling (13% to 49%), and erythema (7% to 42%).<sup>6,7,11,14-16</sup> Fever has also been reported as a common systemic adverse effect to the

qHPV and 9vHPV.<sup>6,14,17</sup> Headache, nausea, dizziness, and fatigue are other systemic adverse effects related to both qHPV and 9vHPV.<sup>6,7,18</sup> Common adverse events of 2vHPV include myalgia, gastrointestinal symptoms and arthralgia.<sup>11</sup>

### Pivotal Trials

Clinical trials demonstrating the efficacy of the HPV vaccine as well as trials supporting the bridging of the 9vHPV to specific populations have been conducted. Table 4 summarizes the clinical implications of pivotal trials involving the qHPV and 9vHPV.

**Table 4: Pivotal Trials Regarding the Quadrivalent and 9-valent HPV Vaccines**

Trial <sup>a</sup>	Vaccine Studied	Study Design	Study Population	Study Findings	Clinical Implications
Garland SM, Hernandez-Avila M, Wheeler CM, <i>et. al.</i> (2007) <sup>14</sup>	qHPV	International, multicentered, randomized, double-blind, placebo-controlled	5,455 women Age 16 to 24 years	<ul style="list-style-type: none"> <li>• 73% effective (95% CI, 58-83) when all combined</li> <li>• 55% effective (95% CI, 40-66) when all grades of cervical lesions were combined</li> <li>• No cancers associated with any qHPV identified</li> </ul>	qHPV is highly effective in preventing anogenital warts, VIN, VaIN, and CIN associated with HPV types 6, 11, 16, and 18 in young women.
The FUTURE II Study Group (2007) <sup>15</sup>	qHPV	International, multicentered, randomized, double-blind, placebo-controlled	12,167 women Age 15 to 26 years	<ul style="list-style-type: none"> <li>• 98% effective (95% CI, 86-100) in preventing HPV type 16/18-related high grade cervical lesions in per-protocol susceptible population</li> <li>• 44% effective (95% CI, 26-58) in preventing HPV type 16/18-related high grade cervical lesions in intention-to-treat population</li> </ul>	qHPV is highly effective in preventing HPV 16 or 18-related CIN grade 2 or 3 and AIS in young women who had not been previously exposed to either HPV 16 or 18.
Reisinger KS, Block SL, Lazcano-Ponce E, <i>et. al.</i> (2007) <sup>19</sup>	qHPV	International, multicentered, randomized, double-blind, placebo-controlled	1,781 sexually naïve children Age 9 to 15 years	<ul style="list-style-type: none"> <li>• &gt;99.5% of subjects had seroconverted by 1 month after completing the 3-dose series, regardless of gender</li> <li>• GMTs and seroconversion rates in boys were noninferior to those in girls for each vaccine component (<math>P&lt;0.001</math>)</li> </ul>	qHPV induced persistent anti-HPV serological responses in majority of subjects for at least 12 months, was generally well tolerated, and supports universal vaccination of adolescents.
Ferris D, Samakoses R, Block SL, <i>et. al.</i> (2014) <sup>20</sup>	qHPV	Long-term study data; *Placebo subjects from Trial #19 received qHPV at month-30	1,781 sexually naïve children Age 9 to 15 years	<u>EVG</u> <ul style="list-style-type: none"> <li>• Female: no cases of qHPV-related diseases observed. 2 cases of HPV16-related persistent infection of &gt;4 months' duration was detected.</li> <li>• Male: no cases of qHPV-related diseases were observed. 1 case of HPV6-related and 1 case of HPV16-related persistent infection of &gt;4 months' duration was detected.</li> </ul>	qHPV demonstrated clinical effective protection from HPV 6, 11, 16, and 18-related infection and disease and sustained antibody titers over 8 years in adolescents.
Munoz N, Manalastas R, Pitisuttithum P, <i>et. al.</i> (2009) <sup>21</sup>	qHPV	International, multicentered, randomized, double-blind, placebo-controlled	3,819 women Age 24 to 45 years	<ul style="list-style-type: none"> <li>• Vaccine efficacy against combined incidence of infection of at least 6 months' duration and cervical and external genital disease related to qHPV types – 90.5% (95% CI, 73.7-97.5)</li> <li>• Prevention of vaccine-type-related infection alone – 92.6% (95% CI, 76.9-98.5)</li> </ul>	qHPV is highly effective against infection of at least 6 months' duration, cervical disease, and external genital diseases related to HPV 6, 11, 16, and 18 in women 24 to 45 years.
Castellsague X, Munoz N, Pitisuttithum P, <i>et. al.</i> (2011) <sup>22</sup>	qHPV	End of study data from Trial #21 after a median follow-up of 4 years	3,819 women Age 24 to 45 years	<ul style="list-style-type: none"> <li>• Vaccine efficacy against combined incidence of persistent infection, CIN, or EGL related to qHPV types:</li> <li>• Per-protocol efficacy – 88.7% (95% CI, 78.1-94.8),</li> <li>• Naïve to the relevant HPV type – 79.9% (95% CI, 69.4-87.3)</li> <li>• Intention-to-treat – 47.2% (95% CI, 33.5-58.2)</li> <li>• Women aged 24-34 years – 91.3% (95% CI, 78.4-97.3)</li> <li>• Women aged 35-45 years – 83.8% (95% CI, 57.9-95.1)</li> </ul>	qHPV demonstrates efficacy, immunogenicity, and safety in women between the ages of 24 and 45 years based on final 4-year follow-up data.

Table 4 continued on next page

**Table 4: Pivotal Trials Regarding the Quadrivalent and 9-valent HPV Vaccines Continued**

Trial <sup>a</sup>	Vaccine Studied	Study Design	Study Population	Study Findings	Clinical Implications
Giuliano AR, Palefsky JM, Goldstone S, <i>et al.</i> (2011) <sup>17</sup>	qHPV	International, multicentered, randomized, double-blind, placebo-controlled	4,065 males Age 16 to 26 years	• The qHPV vaccine efficacy was 65.5% (95% CI 45.8 – 78.6) for lesions related to qHPV types	qHPV is effective in preventing the development of external genital lesions associated with HPV types 6, 11, 16, and 18 in males 16 to 26 years.
Palefsky JM, Giuliano AR, Goldstone S, <i>et al.</i> (2011) <sup>16</sup>	qHPV	Substudy of Giuliano AR, Palefsky JM, Goldstone S, <i>et al.</i> (2011) <sup>17</sup>	602 MSM Age 16 to 26 years	• Vaccine efficacy against AIN due to any HPV type: 25.7% (95% CI, -1.1 – 45.6) • Vaccine efficacy against AIN due to qHPV types: 50.3% (95% CI, 25.7 – 67.2) • Significant reductions in both AIN of grade 1 (49.6%; 95% CI, 21.2 – 68.4) and AIN of grade 2 or 3 (54.2%; 95% CI, 18.0 – 75.3)	qHPV is effective in preventing HPV 6, 11, 16, and 18-related AIN of grades 1, 2, or 3, and persistent anal infection with each of the four HPV strains, and detection of HPV 6, 11, 16, or 18 DNA in both the per protocol and intention-to-treat populations among MSM.
Hillman RJ, Giuliano AR, Palefsky JM, <i>et al.</i> (2012) <sup>23</sup>	qHPV	Immunogenicity results of Giuliano AR, Palefsky JM, Goldstone S, <i>et al.</i> (2011) <sup>17</sup>	3,463 HM Age 16 to 23 years and 602 MSM Age 16 to 26 years (see Trial #17)	• 97.4% of subjects seroconverted for qHPV types by month-7 with anti-qHPV types GMTs reaching peak values 1 month after dose 3 (month-7).	qHPV is highly immunogenic for all vaccine types in HM age 16 to 23 years and MSM age 16 to 26 years. HM had higher GMT levels for all vaccine HPV types at their peak than did MSM.
Joura EA, Giuliano AR, Iversen O-E, <i>et al.</i> (2015) <sup>18</sup>	qHPV	International, multicentered, randomized, double-blind, phase 2b-3	14,215 women Age 16 to 26 years	• Incidence of high grade cervical, vulvar, and vaginal disease among all participants: 14.0 per 1000 person years in both the qHPV and 9vHPV groups • Number of cases of infection and disease associated with HPV 6, 11, 16, and 18 was similar in the 9vHPV and the qHPV group.	9vHPV prevented cervical, vulvar, and vaginal disease, and persistent infection related to HPV-31, 33, 45, 52, and 58. Subjects who received the 9vHPV had antibody responses to HPV 6, 11, 16, and 18 that were noninferior to subjects who received the qHPV.
Damme PV, Olsson SE, Block S, <i>et al.</i> (2015) <sup>24</sup>	qHPV	International, multicentered	3,074 subjects: 9 to 15 year old girls (N=1,935), 9 to 15 year old boys (N=669), 16 to 26 year old females (N=470)	• GMT responses in girls and boys were noninferior to those of young women. • Month 7 GMTs in girls and boys were higher than those in young women • >99% of participants seroconverted by month 7 to all 9 HPV types, meeting the criterion for noninferiority antibody responses	The antibody responses in 9 to 15 year old boys and girls were noninferior to those observed in 16 to 26 year old women. Therefore, this study supports the bridging of efficacy findings for the 9vHPV from 16 to 26 year old women to 9 to 15 year old boys and girls.
Castellsague X, Giuliano AR, Goldstone, <i>et al.</i> (2015) <sup>25</sup>	qHPV	International, multicentered	1,106 HM, 313 MSM and 1,101 women Age 16 to 26 years	• All 9 vaccine HPV types: month-7 GMTs in HM were higher than those in women or MSM. • >99% of participants seroconverted by month 7 to all 9 HPV types in all 3 groups. • GMT responses in HM were non-inferior to those in young women.	The antibody response in HM age 16 to 26 years was noninferior to those observed in women age 16 to 26 years. Study supports the bridging of efficacy findings from men to women ages 16 to 26 years. Antibody responses for all vaccine HPV types were numerically lower in MSM than in heterosexual men and women.

<sup>a</sup>Refer to corresponding reference for citation

**Abbreviations:** 9vHPV-nine-valent human papillomavirus vaccine, AIN-anal intraepithelial neoplasia, AIS-adenocarcinoma in situ, CIN-cervical intraepithelial neoplasia, EGL-external genital lesions, EAG-external anovaginal, EVG - early vaccination group, GMT-geometric mean titer, HM-heterosexual men, MSM-men who have sex with men, qHPV-quadrivalent human papillomavirus vaccine, VaIN-vaginal intraepithelial neoplasia, VIN-vulvar intraepithelial neoplasia.

### Role of the Pharmacist

Recent findings have indicated a slight increase in the number of boys and girls aged 13 to 17 receiving HPV vaccinations. The CDC's 2014 National Immunization Survey-Teen reveals that 60% of adolescent girls and 42% of adolescent boys have received one or more doses of the HPV vaccines, this is a 3% increase in adolescent girls and 8% increase in adolescent boys from 2013. However, the number of preteens vaccinated against HPV is still not sufficient; 4 out of 10 adolescent girls and 6 out of 10 adoles-

cent boys have not initiated the HPV vaccination series.<sup>26</sup> These statistics suggest that patients and parents may not be aware of the importance of these vaccines. In 47 states, including New Jersey, Connecticut, Massachusetts, and Maryland, as well as the District of Columbia and Puerto Rico, pharmacists are authorized to administer HPV vaccines. However, states have varying age limitations on patients that pharmacists can vaccinate. States also vary in their requirements for a prescription to vaccinate.<sup>27</sup> In a study evaluating state laws and regulations regarding pharmacists' authorization to administer HPV vaccines, the authors conclude that pharmacists' ability to administer the HPV vaccine varies by state and that these regulations result in underuse of pharmacists in the efforts to expand HPV vaccination.<sup>28</sup> Pharmacists are accessible and knowledgeable health care providers who can provide patients, parents, and other health care providers with education about the benefits of the HPV vaccines, hopefully leading to an increase in the number of adolescents who are vaccinated.

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## Practice Spotlight:

### Editor's Commentary - Spotlight on Women in Pharmacy

As many are aware, pharmacy has a *long* history tracing back to the Dawn of Man. While growing up, I didn't see many women pharmacists. In the movies, 'Doc' of the Wild West, was depicted as a man in a white coat. 'Doc' dispensed medications to the local town's people – laudanum, digitoxin, and whiskey were used to help what ailed them. I wanted to learn about some of the *women* who have had a great influence in pharmacy.

Interestingly, the American Pharmacy Association (APhA) published an intriguing list of twenty women and pharmaceutical organizations founded by women.<sup>1</sup> Katherine "Kay" Keating (1922-2009), a pharmacist, was the first woman to earn the ranks of Captain in the Navy Medical Corps. Mary Munson Runge (1928-2014) is recognized as the first African American and woman to serve as the president of APhA in 1979.<sup>1</sup> During her tenure as president she established the Task Force on Women in Pharmacy and an Office of Women's Affairs with the APhA. As a testament to her contributions to the profession, Runge, was the recipient of the APhA Hugo H. Schaefer Award in 1996!<sup>1</sup> Elizabeth Gooking Greenleaf (1681-1782) is recognized as the very first female pharmacist in America, residing in the New England, she owned a pharmacy, practicing pharmacy during the late 1600s to early 1700s with her husband, who was also a pharmacist.<sup>1</sup> And while Elizabeth Gooking Greenleaf is noted as the first Caucasian female pharmacist; Dr. Ella Nora Phillips Stewart (1893-1987) is reported to be one of the first female African American pharmacists in the United States. Dr. Stewart's matriculation through the University of Pittsburgh was significant, in that, her admission in 1914 made her the first African American student allowed to study at the university; thus desegregating the university. In 1916, Dr. Stewart earned her Doctor in Philosophy (Ph.D.) and after passing her state examination, became recognized as a registered pharmacist.<sup>2</sup> The role of women in pharmacy can also be indirect. Albeit Henrietta Lacks (1920-1951) was not a pharmacist, her cancerous cells have had an impact on pharmacy greatly by initiating feverish research in cancer research and the development of vaccinations. Mrs. Lacks, while in Johns Hopkins's for treatment for her cervical cancer, had two pieces of her cervix removed – a healthy and a cancerous-portion by Dr. George Otto Gey. He sent the specimens to his pathology lab where it was found that Mrs. Lacks' cells when

tested could be kept alive, and we now know that these cells can be grown forever. Mrs. Lacks' cells are known as the HeLa cells and are used in many aspects of biomedical research including AIDS, gene mapping and vaccines, such as the human papilloma vaccine.<sup>3</sup> Dr. Harald zur Hausen found that Mrs. Lacks' tissues tested positive for Human Papilloma Virus (HPV) 15 and 16, both of which cause cervical cancer, leading to the development of the HPV vaccine.<sup>4</sup> Henrietta Lacks will forever be known in the realm of medicine for her contribution to the sciences. The use of her cells, all over the world in research, are definitely not without controversy as she (nor her estate) has ever given permission for their use, and while the legal aspects of the use of the HeLa cells is not part of this discussion, we must always remember that there are laws in place to ensure proper utilization of human tissue.

There are many women that we can spotlight in pharmacy; this was but a snapshot of a few women who have made an impact on pharmacy as we know it. I'm sure that you can name a litany of outstanding women too! I wanted to take this time to acknowledge these extraordinary women in our pharmacy past and thank them all for their brilliance and resilience. To our women of pharmacy today and tomorrow, we look forward to new knowledge and discoveries that will revolutionize healthcare.

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## New Drugs: Cosentyx, Ibrance, Lenvima, and Unituxin

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*Dr. Thomas A. Gossel has no relevant financial relationships to disclose.*

**Goal.** The goal of this lesson is to provide information on four new drugs: dinutuximab (Unituxin<sup>TM</sup>), lenvatinib (Lenvima<sup>TM</sup>), palbociclib (Ibrance<sup>®</sup>), and secukinumab (Cosentyx<sup>TM</sup>).

**Objectives.** At the completion of this activity, the participant will be able to:

1. recognize signs and symptoms, and key features of targeted pathologies for these new drugs, including information on their prevalence in the population;
2. recognize important therapeutic uses for the drugs and their applications in specified pathologies;
3. select the indication(s), pharmacologic action(s), clinical applications, dosing regimens, mode of administration, and availability for each drug;
4. demonstrate an understanding of adverse effects and toxicity, warnings, precautions, contraindications, and significant drug-drug or drug-food interactions reported for each agent; and
5. list important counseling information to convey to patients and/or their caregivers.

The four new-molecular entity drugs discussed in this lesson have been approved to treat a wide variety of pathologies (Table 1). The lesson provides a brief introduction

to the therapeutic agents, and its depth is not intended to extend beyond an overview of the topic. The reader is, therefore, encouraged to consult the products' full prescribing information leaflet (package insert), FDA-approved *Medication Guide* when available, and other reliable sources for more detailed information.

### Dinutuximab (Unituxin)

Unituxin (yu-ni-TUX-in) is the first approved drug aimed specifically for treatment of patients with high-risk neuroblastoma. It fulfills a critical need by providing a treatment option that prolongs survival in children with this high-risk cancer.

**Indications and Use.** Unituxin is indicated for use in combination with granulocyte-macrophage colony-stimulating factor, interleukin (IL)-2 (IL-2), and 13-cis-retinoic acid (RA) for treatment of pediatric patients with high-risk neuroblastoma who achieve at least a partial response to prior first-line multiagent, multimodality therapy. Multimodality regimens include surgery, autologous stem cell transplantation, chemotherapy, and radiotherapy.

**Neuroblastoma.** Neuroblastoma is the most common extracranial solid tumor in childhood, accounting for 6 percent of all childhood cancers in the United States. It is cancer that forms from embryonic (immature) nerve cells, often developing in the adrenal glands, but may also form in the abdomen,

chest, or nerves that run alongside the spine. Neuroblastoma typically occurs in children younger than five years of age. According to the National Cancer Institute, neuroblastoma occurs in approximately one in 100,000 live births. About 90 percent of children are younger than five years at diagnosis. It is slightly more common in boys.

The five-year overall survival for all infants and children with neuroblastoma has increased from 46 percent when diagnosed between 1974 and 1989, to 71 percent when diagnosed between 1999 and 2005. Neuroblastoma has a worse prognosis in adolescents older than 10 years or in adults, regardless of stage or site; and in many cases, it has a more prolonged course when treated with standard doses of chemotherapy. There are racial differences in tumor biology, with African-Americans more likely to have high-risk disease and fatal outcome when compared with Caucasians.

**Mechanism of Action.** Dinutuximab is a monoclonal antibody that binds to the glycolipid GD2. This glycolipid is expressed on neuroblastoma cells and on normal cells of neuroectodermal origin, including the central nervous system and peripheral nerves. Dinutuximab binds to cell surface GD2 and induces cell lysis.

**Efficacy and Safety.** Efficacy and safety of Unituxin were evaluated in a clinical trial of 226 pediatric participants (median age 3.8 years) with high-risk neuro-

**Table 1**  
**Selected new drugs**

Generic (Trade Name)	Distributor	Indication	Dose*	Dosage Form	Most Common Side Effects	Medication Guide <sup>‡</sup>
Dinutuximab (Unituxin)	United Therapeutics Corp	neuroblastoma	17.5 mg/m <sup>2</sup> / day x 4 days	single-use vials for IV infusion 17.5 mg/5mL	(≥25%): pain, pyrexia, thrombocytopenia, lymphopenia, infusion reactions, hypotension, hyponatremia, increased alanine aminotransferase, anemia, vomiting, diarrhea, hypokalemia, urticaria, hypoalbuminemia, increased aspartate aminotransferase, hypocalcemia, capillary leak syndrome, neutropenia	No
Lenvatinib (Lenvima)	Eisai, Inc.	thyroid cancer	24 mg PO daily	4 mg, 10 mg capsules	(≥30%): hypertension, fatigue, diarrhea, arthralgia/myalgia, decreased appetite, weight loss, nausea, stomatitis, headache, vomiting, proteinuria, palmar-plantar erythrodysesthesia syndrome, abdominal pain, dysphonia	No
Palbociclib (Ibrance)	Pfizer Labs	breast cancer	125 mg PO daily x 21 days; off 7 days	75 mg, 100 mg, 125 mg capsules	(≥10%) <sup>§</sup> : neutropenia, leukopenia, fatigue, anemia, URI, nausea, stomatitis, alopecia, diarrhea, thrombocytopenia, decreased appetite, vomiting, asthenia, peripheral neuropathy, epistaxis	No
Secukinumab (Cosentyx)	Novartis Pharmaceuticals Corp	psoriasis	300 mg @ weeks 0, 1, 2, 3, 4; then every 4 weeks	single-use pen, pre-filled syringes, vials for SC injection, 150 mg	(>1%): nasopharyngitis, URI, diarrhea	Yes

\*Recommended dose for most patients

<sup>‡</sup>Availability at the time of publication of this lesson

<sup>§</sup>reported in patients taking Ibrance plus letrozole

blastoma whose tumors shrunk or disappeared after treatment with multiple-drug chemotherapy and surgery followed by additional intensive chemotherapy and who subsequently received bone marrow transplantation support and radiotherapy. Participants were randomly assigned to receive either an oral retinoid drug (RA; isotretinoin), or Unituxin in combination with interleukin-2 and granulocyte-macrophage colony-stimulating factor, both of which are believed to enhance the activity of Unituxin by stimulating the immune system, and RA.

Three years after treatment assignment, 63 percent of participants receiving the Unituxin combination were alive and free of tumor growth or recurrence, compared to 46 percent of participants treated with RA alone. In an updated analysis of survival, 73 percent of participants who received the Unituxin combination were alive compared with 58 percent of those receiving RA alone.

The most common adverse effects are listed in Table 1. The most common serious adverse reactions (≥5 percent) are infections, infusion

reactions, hypokalemia, hypotension, pain, fever, and capillary leak syndrome. Unituxin carries a *Boxed Warning* alerting patients and health care professionals that Unituxin irritates nerve cells, causing severe pain that requires treatment with intravenous narcotics before, during, and after Unituxin infusion, and can also cause nerve damage and life-threatening infusion reactions.

**Warnings and Precautions.** The following **warnings and precautions** are listed:

- Capillary leak syndrome and

**Table 2**  
**Patient counseling information for Unituxin\***

Inform patients and/or caregivers:

- that there is a risk of serious infusion reactions and anaphylaxis and to immediately report any signs or symptoms, such as facial or lip swelling, urticaria, difficulty breathing, lightheadedness, or dizziness that occur during or within 24 hours following the infusion;
- of the risk of severe pain and peripheral sensory and motor neuropathy, and to promptly report severe or worsening pain and signs and symptoms of neuropathy such as numbness, tingling, burning, or weakness;
- of the risk of capillary leak syndrome and to immediately report any signs or symptoms;
- of the risk of hypotension during the infusion and to immediately report any signs or symptoms;
- of the risk of infection following treatment, and to immediately report any signs or symptoms;
- of the risk of neurological disorders of the eye and to promptly report signs or symptoms such as blurred vision, photophobia, ptosis, diplopia, or unequal pupil size;
- of the risk of bone marrow suppression, and to promptly report signs or symptoms of anemia, thrombocytopenia, or infection;
- of the risk of electrolyte abnormalities including hypokalemia, hyponatremia, and hypocalcemia, and to report any signs or symptoms such as seizures, heart palpitations, and muscle cramping;
- of the risk of hemolytic uremic syndrome and to report any signs or symptoms such as fatigue, dizziness, fainting, pallor, edema, decreased urine output, or hematuria;
- (females of reproductive potential) that there is a potential risk to the fetus if Unituxin is administered during pregnancy and the need for use of effective contraception during, and for at least two months after completing therapy.

\*A complete list of counseling information is available in the product's Prescribing Information leaflet.

**hypotension:** Administer required prehydration and monitor patients closely during treatment. Depend-

ing upon severity, manage by interruption, infusion rate reduction, or permanent discontinuation;

- **Infection:** Temporarily interrupt until resolution of systemic infection;

- **Neurological disorders of the eye:** Interrupt for dilated pupil with sluggish light reflex or other visual disturbances and permanently discontinue for recurrent eye disorders or loss of vision;

- **Bone marrow suppression:** Monitor peripheral blood counts during Unituxin therapy;

- **Electrolyte abnormalities:** Monitor serum electrolytes closely each day during therapy with Unituxin;

- **Atypical hemolytic uremic syndrome:** Permanently discontinue Unituxin and institute supportive management;

- **Embryo-fetal toxicity:** Based on its mechanism of action, may cause fetal harm when given to a pregnant woman. Advise females of reproductive potential of potential risks to a fetus and to use effective contraception during and for two months after the last dose of Unituxin.

A history of anaphylaxis to dinutuximab is the only **contraindication**.

**Drug Interactions.** No drug-drug interaction studies have been conducted with dinutuximab.

**Administration, Dosing, and Availability.** The recommended dose of dinutuximab is 17.5 mg/m<sup>2</sup>/day administered as a diluted intravenous infusion over 10 to 20 hours for four consecutive days for up to five cycles. Prior to initiation of each dose of dinutuximab, administer required intravenous hydration and premedication with antihistamines, analgesics, and antipyretics.

Unituxin is available as an intravenous injection containing 17.5 mg/5 mL in a single-use vial. Vials should be stored in a refrigerator at 2°C to 8°C (36°F to 46°F), protected from light by storing in the outer carton, and neither be frozen nor shaken.

**Patient Counseling.** Specific

points for patient counseling are summarized in Table 2.

### Lenvatinib (Lenvima)

Development of new therapies to assist patients with refractory disease is of primary importance. Lenvima's approval offers patients an additional therapeutic option to help slow the progression of differentiated thyroid cancer (DTC).

**Indications and Use.** Lenvima (lenv-VEEMA) is indicated for the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer.

**Differentiated Thyroid Cancer.** Carcinoma of the thyroid is an uncommon cancer but the most common malignancy of the endocrine system. Over the past three decades, thyroid cancer has been increasing in the United States, Canada, and some European countries. In the United States, its incidence has increased more than any other cancer. DTC accounts for more than 90 percent of all thyroid malignancies and includes papillary, follicular, and Hürthle cell histologies. Thyroid cancer affects women more commonly than men, estimated to be 9.1 per 100,000 females and 2.9 per 100,000 males. Onset usually occurs between 25 and 65 years of age.

DTC is ordinarily highly treatable and usually curable. Standard therapies for patients with advanced DTC include surgery, radioactive iodine, and thyroid-stimulating hormone (TSH) suppression. Although DTC is associated with low mortality, disease recurrence is high, at 20 to 30 percent, or even higher in some subgroups of patients. In most patients with DTC, however, recurrence is low.

The National Cancer Institute estimates that 62,450 Americans will be diagnosed with thyroid cancer with 1,950 deaths from the disease in 2015. Although most patients with DTC have a favorable prognosis with standard treatments, 10 to 15 percent of patients will develop disease refractory to

radioactive iodine therapy. For decades, standard therapy for radioactive iodine-refractory DTC consisted of cytotoxic chemotherapy with doxorubicin (Adriamycin, Doxil), with unsatisfactory results and serious side effects. These patients have a median overall survival of 2.5 to 3.5 years.

#### Mechanism of Action.

Lenvatinib is a receptor tyrosine kinase (RTK) inhibitor that inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4). It also inhibits other RTKs that have been implicated in pathogenic angiogenesis (formation and development of blood vessels), tumor growth, and cancer progression. Interference with blood supply into a cancerous growth is a deterrent to continued tumor growth.

**Efficacy and Safety.** Efficacy and safety were demonstrated in 392 participants (with progressive, radioactive iodine-refractory DTC) who were randomly assigned to receive either Lenvima or placebo. Study results showed Lenvima-treated participants lived a median of 18.3 months without their disease progressing (progression-free survival), compared to a median of 3.6 months for participants who received placebo. Additionally, 65 percent of participants treated with Lenvima experienced a reduction in tumor size, compared to 2 percent of participants who received placebo. A majority of participants randomly assigned to receive the placebo were treated with Lenvima upon disease progression.

The most common adverse effects noted in clinical trials are listed in Table 1. Serious adverse effects included cardiac failure; arterial thromboembolic events; hepatotoxicity; renal failure and impairment; gastrointestinal perforation in the wall of the stomach or intestines, or fistula formation (abnormal connection between two parts of the stomach or intestines); QT interval prolongation; hypocalcemia; the simultaneous occurrence of headache, confusion, seizures

and visual changes (Reversible Posterior Leukoencephalopathy Syndrome); hemorrhage; risks to an unborn child if a patient becomes pregnant during treatment; and impaired suppression of production of TSH.

#### Warnings and Precautions.

The following **warnings** and **precautions** are listed:

- **Hypertension:** Control blood pressure prior to treatment with Lenvima. Withhold Lenvima for Grade 3 hypertension despite optimal antihypertensive therapy. Discontinue for life-threatening hypertension;
- **Cardiac failure:** Monitor for clinical symptoms or signs of cardiac decompensation. Withhold Lenvima for Grade 3 cardiac dysfunction. Discontinue for Grade 4 cardiac dysfunction;
- **Arterial thromboembolic events:** Discontinue Lenvima following an arterial thromboembolic event;
- **Hepatotoxicity:** Monitor liver function tests before initiation of Lenvima, and periodically throughout treatment. Withhold Lenvima for Grade 3 or greater liver impairment. Discontinue for hepatic failure;
- **Proteinuria:** Monitor for proteinuria before initiation of, and periodically throughout treatment with Lenvima. Withhold Lenvima for  $\geq 2$  grams of proteinuria per 24 hours. Discontinue for nephrotic syndrome;
- **Renal failure and impairment:** Withhold Lenvima for Grade 3 or 4 renal failure/impairment;
- **Gastrointestinal perforation and fistula formation:** Discontinue Lenvima in patients who develop gastrointestinal perforation or life-threatening fistula;
- **QT interval prolongation:** Monitor and correct electrolyte abnormalities in all patients. Withhold Lenvima for development of Grade 3 or greater QT interval prolongation;
- **Hypocalcemia:** Monitor blood calcium levels at least monthly and replace calcium as necessary;
- **Reversible posterior leukoen-**

**Table 3**  
**Patient counseling information for Lenvima\***

Inform patients:

- to undergo regular blood pressure monitoring and to contact their healthcare provider if blood pressure is elevated;
- that Lenvima can cause cardiac dysfunction and to immediately contact their healthcare provider if they experience any clinical symptoms of cardiac dysfunction such as shortness of breath or swelling of ankles;
- to seek immediate medical attention for new onset chest pain or acute neurologic symptoms consistent with heart attack or stroke;
- that they will need to undergo lab tests to monitor for liver function and to report any new symptoms indicating hepatic toxicity or failure;
- that they will need to undergo regular lab tests for kidney function and protein in the urine;
- that Lenvima can increase the risk of gastrointestinal perforation or fistula and to seek immediate medical attention for severe abdominal pain;
- that Lenvima can increase the risk for bleeding and to contact their healthcare provider for bleeding or symptoms of severe bleeding;
- (females of reproductive potential) of the risk to a fetus and to inform their healthcare provider of a known or suspected pregnancy. Advise them to use effective contraception during treatment with Lenvima and for at least two weeks following completion of therapy. If breastfeeding, they should discontinue breastfeeding during treatment with Lenvima.

\*A complete list of counseling information is available in the product's Prescribing Information leaflet.

*cephalopathy syndrome (RPLS):*  
Withhold Lenvima for RPLS until fully resolved;

*• Hemorrhagic events:* Withhold Lenvima for Grade 3 hemorrhage. Discontinue for Grade 4 hemorrhage;

*• Impairment of thyroid stimulating hormone suppression:* Monitor TSH levels monthly and adjust thyroid replacement medication as needed in patients with DTC;

*• Embryofetal toxicity:* Based

on its mechanism of action, Lenvima may cause fetal harm. Advise females of potential risk to a fetus and use of effective contraception during Lenvima use and for at least two weeks following completion of therapy.

There are no **contraindications** listed.

**Drug Interactions.** No dose adjustment of lenvatinib is recommended when co-administered with CYP3A, P-glycoprotein (P-gp), and breast cancer resistance protein (BCRP) inhibitors, and CYP3A and P-gp inducers.

**Administration, Dosing, and Availability.** The recommended dose of Lenvima is 24 mg once daily taken with or without food. In patients with severe renal or hepatic impairments, the dose is 14 mg once daily. Dosing may continue until disease progression or until unacceptable toxicity occurs.

Lenvima is available in 4 mg and 10 mg capsules.

**Patient Counseling.** Specific points for patient counseling are summarized in Table 3.

### Palbociclib (Ibrance)

The addition of targeted agents to current therapy has provided the potential for significant clinical benefit for patients with metastatic breast cancer. Several novel therapies have been developed that offer affected women renewed hope for healing. Palbociclib selectively interferes with the critical components of the cell cycle regulatory machinery in breast cancer.

**Indications and Use.** Ibrance (EYE-brans) is indicated in combination with letrozole (Femara) for the treatment of postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer as initial endocrine-based therapy for their metastatic disease.

**Breast Cancer.** Breast cancer is the most frequent female malignancy worldwide, and the second most common cancer in the U.S. after prostate cancer. Breast cancer forms in the breast tissue and in

advanced cases, spreads to surrounding normal tissue. The median age at diagnosis is 61 years. The National Cancer Institute estimates that 232,670 American women were diagnosed with breast cancer and 40,000 died from the disease in 2014. Approximately 12.3 percent of women will have a positive diagnosis at some point during their lifetime.

Three major therapeutic approaches used today to treat or control breast cancer are surgical removal of primary tumors, irradiation of cancer cells to control their growth, and anticancer drugs to kill cancer cells or inhibit their proliferation. Notably, surgery or radiotherapy still requires chemotherapy to eradicate remaining malignancy cells and impede relapses.

Anticancer drugs are based on three therapeutic approaches: (1) classical chemotherapy to stop cell proliferation by the indiscriminate targeting of rapid cell division in the body, (2) hormone therapy that stops cancer cell growth by targeting the receptors and downstream signaling molecules of hormones pivotal for proliferation of these cells, and (3) targeted therapy where signaling pathways deregulated in primary breast tumors are specifically targeted. Interestingly, frequent advances in the understanding of breast cell microbiology spotlight the tumor microenvironment as a significant player in breast carcinogenesis and have provided new avenues for targeted therapy.

### Mechanism of Action.

Palbociclib is an orally available inhibitor of cyclin-dependent kinase (CDK) 4 and 6. Cyclin D1 and CDK4/6 are downstream of signaling pathways that lead to cellular proliferation contributing to sustained tumor growth.

**Efficacy and Safety.** Efficacy and safety were demonstrated in 165 postmenopausal women with ER-positive, HER2-negative advanced breast cancer who had not received previous treatment for advanced disease. Clinical study participants were randomly as-

signed to receive Ibrance in combination with letrozole or letrozole alone. Participants treated with Ibrance plus letrozole lived about 20.2 months without their disease progressing (progression-free survival), compared to about 10.2 months seen in participants receiving only letrozole. Information on overall survival is not available at this time.

The most common adverse effects are listed in Table 1. The most frequently reported serious adverse reactions in patients receiving palbociclib plus letrozole are pulmonary embolism (4 percent) and diarrhea (2 percent).

**Warnings and Precautions.** The following **warnings** and **precautions** are listed:

- **Neutropenia:** Monitor complete blood count prior to start of Ibrance therapy and at the beginning of each cycle as well as on Day 14 of the first two cycles, and as clinically indicated;

- **Infections:** Monitor for signs and symptoms of infection and withhold dosing as medically appropriate;

- **Pulmonary embolism:** Monitor patients for signs and symptoms of pulmonary embolism and treat as medically appropriate;

- **Embryo-fetal toxicity:** The drug can cause fetal harm. Advise females of potential risk to a fetus and to use effective contraception.

There are no **contraindications** listed.

**Drug Interactions.** Palbociclib is metabolized primarily by CYP3A and sulfotransferase (SULT) enzyme SULT2A1. Avoid coadministration with strong CYP3A *inhibitors* (e.g., clarithromycin, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, verapamil, voriconazole). Avoid grapefruit or grapefruit juice during Ibrance treatment. If coadministration of Ibrance with a strong CYP3A inhibitor cannot be avoided, reduce the dose of Ibrance.

Avoid concomitant use of

**Table 4**  
**Patient counseling information for Ibrance\***

Inform patients:

- to immediately report any signs or symptoms of myelosuppression or infection, such as fever, chills, dizziness, shortness of breath, weakness or any increased tendency to bleed and/or to bruise;
- to immediately report any signs or symptoms of pulmonary embolism, such as shortness of breath, chest pain, tachypnea, and tachycardia;
- to take Ibrance with food and swallow the capsules whole. No capsule should be ingested if it is broken, cracked, or otherwise not intact;
- that Ibrance may interact with grapefruit, thus patients should not consume grapefruit products while on treatment with Ibrance;
- to avoid strong CYP3A inhibitors and strong CYP3A inducers;
- to inform their healthcare providers of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products;
- that if they vomit or miss a dose, an additional dose should not be taken that day. The next prescribed dose should be taken at the usual time;
- (females of reproductive potential) to use effective contraception during Ibrance therapy and for at least two weeks after the last dose. Advise females to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, during treatment with Ibrance.

\*A complete list of counseling information is available in the product's Prescribing Information leaflet.

strong CYP3A *inducers* (e.g., phenytoin, rifampin, carbamazepine, St. John's Wort). Coadministration of moderate CYP3A inducers may also decrease the plasma exposure of Ibrance; thus, avoid concomitant use of moderate CYP3A *inducers* (e.g., bosentan, efavirenz, etravirine, modafinil, nafcillin).

Coadministration of midazolam with multiple doses of Ibrance increased the midazolam plasma exposure by 61 percent in healthy subjects, compared with administration of midazolam alone. The

dose of a sensitive CYP3A substrate with a narrow therapeutic index (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, everolimus, fentanyl, pimozide, quinidine, sirolimus, tacrolimus) may need to be reduced as palbociclib may increase their exposure.

**Administration, Dosing, and Availability.** The recommended starting dose of Ibrance is 125 mg daily taken with food for 21 days, followed by seven days off treatment to comprise a complete cycle of 28 days, in combination with letrozole 2.5 mg once daily given continuously throughout the 28-day cycle. Patients should be encouraged to take their dose at approximately the same time each day. Dosing interruption and/or dose reduction are recommended based on individual safety and tolerability.

Ibrance is available in 75 mg, 100 mg, and 125 mg capsules.

**Patient Counseling.** Specific points for patient counseling are summarized in Table 4.

**Secukinumab (Cosentyx)** Conventional systemic therapies for plaque psoriasis have not fully met the needs of patients, and current biologic treatments, although generally well tolerated, have a still-developing long-term safety profile. Studies conducted in patients with plaque psoriasis have provided evidence that secukinumab may be safe and efficacious as a potential treatment for this disorder.

**Indications and Use.** Cosentyx (koe-SEN-tix) is indicated for treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.

**Psoriasis.** Psoriasis is a common skin condition that causes patches of skin redness and irritation. It is an autoimmune disorder of genetic basis, and thus occurs more commonly in persons with a family history of the disease, and most often begins in people between the ages of 15 and 35. The estimated worldwide population

prevalence is 1 to 3 percent.

The most common form is plaque psoriasis, which accounts for 90 percent of cases. In plaque psoriasis, patients develop thick, red skin with flaky, silver-white patches called scales. Patches frequently occur on the elbows, knees, palms of the hands and soles of the feet, and midsection of the trunk; but can appear anywhere, including on the scalp. The lesions may vary in severity from minor localized patches to complete body coverage. Lesions may be accompanied by intense itching, swelling, and pain. While psoriasis may appear to be contagious, it is not. It is a life-long condition that may regress for long periods and then reappear later.

Psoriasis imposes a major impact on patient psychosocial status and quality of life. The disease also carries an increased risk of comorbidities including psoriatic arthritis, uveitis, cardiovascular disease, the metabolic syndrome as a whole and its individual components, and inflammatory bowel disease, which in severe cases, can reduce life expectancy. Recent studies also showed an increased prevalence of celiac disease, nonalcoholic fatty liver disease, and erectile dysfunction in patients suffering from psoriasis. Preliminary epidemiological data suggest that adequate treatment of psoriasis could reduce the incidence of these comorbidities.

#### Mechanism of Action.

Secukinumab is a high affinity, fully human IgG1 monoclonal antibody that selectively binds with and neutralizes the protein interleukin 17A (IL-17A), a naturally occurring cytokine that is involved in inflammatory and immune responses. By binding to IL-17A, secukinumab prevents it from binding to its receptor, and thus inhibits its ability to trigger the inflammatory response that plays a role in development of plaque psoriasis.

**Efficacy and Safety.** Efficacy and safety were established in four clinical trials with a total of 2,403 participants with plaque psoriasis

**Table 5**  
**Patient counseling information for Cosentyx\***

Inform patients:

- to read the FDA-approved *Medication Guide* before starting Cosentyx therapy and to reread it each time the prescription is renewed;
- that Cosentyx may lower the ability of their immune system to fight infections. Instruct patients of the importance of communicating any history of infections to their healthcare provider and contacting their healthcare provider if they develop any symptoms of infection after receiving Cosentyx;
- to seek immediate medical attention if they experience any symptoms of serious hypersensitivity reactions;
- to refrigerate the Sensoready pens, prefilled syringes, and vials at 2°C to 8°C (36°F to 46°F). Keep the product in its original carton to protect from light until the time of use. Do not freeze. To avoid foaming, do not shake the product.

\*A complete list of counseling information is available in the product's *Medication Guide*.

who were candidates for phototherapy or systemic therapy. Participants were randomly assigned to receive Cosentyx or placebo. The results showed that Cosentyx achieved greater clinical response than placebo, with skin that was clear or almost clear, as assessed by scoring of the extent, nature and severity of psoriatic changes of the skin.

Adverse effects are shown in Table 1. The most common ones included diarrhea and upper respiratory infections (URIs).

**Warnings and Precautions.** The following **warnings** and **precautions** are listed:

- **Infections:** Serious infections have occurred. Caution should be exercised when considering the use of Cosentyx in patients with a chronic infection or a history of recurrent infection. If a serious infection develops, discontinue Cosentyx until the infection resolves;

- **Tuberculosis (TB):** Prior to initiating treatment with Cosentyx,

evaluate for TB. Monitor closely for signs and symptoms of active TB during and after treatment;

- **Crohn's disease:** Exacerbations were observed in clinical trials. Caution should be exercised when prescribing Cosentyx to patients with active Crohn's disease;

- **Hypersensitivity reactions:** If an anaphylactic reaction or other serious allergic reaction occurs, discontinue Cosentyx immediately and initiate appropriate therapy. The removable cap of the Cosentyx Sensoready pen and the prefilled syringe contain natural rubber latex, which may cause an allergic reaction in latex-sensitive individuals;

- **Vaccinations:** Prior to initiating therapy with Cosentyx, consider completion of all age-appropriate immunizations according to current immunization guidelines. Patients treated with Cosentyx should not receive live vaccines. Non-live vaccinations received during a course of Cosentyx may not elicit an immune response sufficient to prevent disease.

Serious hypersensitivity reaction to secukinumab or to any of the product's excipients is a **contraindication** to Cosentyx.

**Drug Interactions.** Drug interaction trials have not been conducted with Cosentyx. See warnings/precautions above for coadministration with vaccines.

**Administration, Dosing, and Availability.** The recommended dose of Cosentyx is 300 mg by subcutaneous injection at weeks 0, 1, 2, 3, and 4; followed by 300 mg every four weeks. For some patients, a dose of 150 mg may be acceptable. Injections should be administered at a different anatomic location (such as upper arms, thighs or any quadrant of the abdomen) than the previous injection, and not into areas where the skin is tender, bruised, erythematous, indurated or affected by psoriasis.

The drug is available in a single-use Sensoready pen and prefilled syringe each containing 150 mg/mL, and in a single-use vial containing 150 mg lyophilized pow-

der for reconstitution by a health-care professional only.

**Patient Counseling.** An FDA-approved *Medication Guide* must be dispensed with each new or refill prescription for Cosentyx. Specific points for counseling are summarized in Table 5.

## Overview and Summary

The new drugs discussed in this lesson each share an important therapeutic option over previously available agents approved to treat their indicated pathologies. These new drugs are all targeted agents whose mechanism of action is directed to modulation of a specific intracellular reaction, versus activity upon less specific systems. They promise additional relief to patients experiencing these illnesses.

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This lesson is a knowledge-based CPE activity and is targeted to pharmacists in all practice settings.

**Program 0129-0000-15-011-H01-P**

Release date: 11-15-15

Expiration date: 11-15-18

CE Hours: 1.5 (0.15 CEU)

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# continuing education quiz

## New Drugs: Cosentyx, Ibrance, Lenvima, and Unituxin

1. Unituxin is indicated for use with all of the following EXCEPT:

- a. 13-cis-retinoic acid.
- b. letrozole.
- c. interleukin-2.
- d. granulocyte-macrophage colony-stimulating factor.

2. Neuroblastomas often develop in the:

- a. adrenal glands.
- b. kidney.
- c. liver.
- d. lung.

3. All of the following are characteristics of thyroid cancer EXCEPT:

- a. it is an uncommon cancer.
- b. it is the most common malignancy of the endocrine system.
- c. it affects men more commonly than women.
- d. onset usually occurs between the ages of 25 and 65.

4. The mechanism of action of lenvatinib is inhibition of:

- a. glycolipid GD2.
- b. cyclin-dependent kinase 4 and 6.
- c. vascular endothelial growth factor receptors.
- d. interleukin-17A.

5. All of the following are symptoms of Reversible Posterior Leukoencephalopathy Syndrome EXCEPT:

- a. visual changes.
- b. hemorrhage.
- c. headache.
- d. confusion.

6. The recommended daily dose of Lenvima in patients with severe renal impairment is:

- a. 5 mg.
- b. 8 mg.
- c. 14 mg.
- d. 24 mg.

7. Patients taking Lenvima should be informed that:

- a. it may increase the risk of capillary leak syndrome.
- b. females of reproductive potential should use effective contraception for at least two months following the final dose.
- c. it should not be taken on an empty stomach.
- d. it may increase the risk of gastrointestinal fistula formation.

• • • • • Completely fill in the lettered box corresponding to your answer.

1. [a] [b] [c] [d]    6. [a] [b] [c] [d]    11. [a] [b] [c] [d]  
2. [a] [b] [c] [d]    7. [a] [b] [c] [d]    12. [a] [b] [c] [d]  
3. [a] [b] [c] [d]    8. [a] [b] [c] [d]    13. [a] [b] [c] [d]  
4. [a] [b] [c] [d]    9. [a] [b]                14. [a] [b] [c] [d]  
5. [a] [b] [c] [d]    10. [a] [b] [c] [d]    15. [a] [b] [c] [d]

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8. The most serious adverse effects reported in patients taking palbociclib and letrozole are:

- a. pulmonary embolism and diarrhea.
- b. decreased appetite and vomiting.
- c. lymphopenia and neutropenia.
- d. proteinuria and thrombocytopenia.

9. If coadministration of Ibrance with a strong CYP3A inhibitor cannot be avoided, reduce the Ibrance dose.

- a. True
- b. False

10. It is recommended that Ibrance be:

- a. taken on an empty stomach.
- b. taken daily for the 28-day cycle.
- c. taken with letrozole for half the cycle.
- d. taken at the same time each day.

11. Grapefruit products should not be consumed by patients taking:

- a. Ibrance.
- b. Cosentyx.
- c. Unituxin.
- d. Lenvima.

12. Which of the following forms of psoriasis accounts for 90 percent of the cases?

- a. Erythrodermic
- b. Gluttate
- c. Plaque
- d. Pustular

13. The proposed mechanism of action of secukinumab is thought to be due to antagonism of:

- a. glycolipid GD2.
- b. interleukin-17A.
- c. cyclin-dependent kinase.
- d. vascular endothelial growth factor.

14. Patients treated with which of the following drugs should not receive live vaccines?

- a. Palbociclib
- b. Secukinumab
- c. Lenvatinib
- d. Dinutuximab

15. Which of the following drug's labeling includes a *Boxed Warning* with an alert for nerve damage?

- a. Cosentyx
- b. Ibrance
- c. Lenvima
- d. Unituxin

• • • • •

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# Use of Raltegravir in HIV-Infected Pregnant Women

By:Tae Eun Park, Pharm.D. BCPS and Julie Kalabalik, Pharm.D. BCPS, BCCCP

## Introduction

The rate of perinatal human immunodeficiency virus (HIV) transmission has decreased to 2% or less in the United States and Europe as a result of prenatal HIV counseling and testing, prophylaxis with antiretroviral therapy (ART), delivery via Cesarean section, and avoidance of breastfeeding. One of the most important factors in preventing perinatal HIV transmission involves the initiation of combination ART to reduce viral load (VL) as early on in pregnancy as possible. ART initiation during pregnancy should be implemented regardless of the CD4 cell count or VL. The goal of combination ART in HIV-infected pregnant women is to maintain an undetectable VL throughout pregnancy. Important considerations related to the pharmacological treatment of HIV infection in pregnant women include the prevention of perinatal transmission, drug teratogenicity, and drug pharmacokinetics in pregnancy. This review provides the clinician with a summary of new evidence and guideline recommendations regarding the use of raltegravir in pregnancy. A PubMed search using the terms “raltegravir” and “pregnancy” was conducted, which yielded 44 results. After selecting only original or relevant articles published between 2010 and 2015, the search yielded 19 references summarized in this article.<sup>1</sup>

## Product Information

Raltegravir (Isentress<sup>®</sup>) is an integrase strand transfer inhibitor (INSTI) approved in 2007 for the treatment of HIV-1 infection in patients four weeks of age and older in combination with other antiretroviral agents. Recommended adult dosing for raltegravir is 400 mg by mouth twice daily. Dosing in children and adolescents who weigh at least 25 kg is 400 mg by mouth twice daily. For children at least 3 kg to less than 25 kg, dosing is weight-based. Raltegravir is available as 400 mg film-coated tablets, 100 mg and 25 mg chewable tablets, and 100 mg single-use packet for oral suspension. Most common adverse reactions associated with raltegravir include insomnia, headache, dizziness, nausea, and fatigue. Creatinine kinase elevations, myopathy, skin reactions, and immune reconstitution syndrome have been reported. Patients with phenylketonuria should be warned that the chewable tablets contain phenylalanine. Drugs that inhibit UDP glucuronosyltransferase (UGT) 1A1 may increase raltegravir levels and UGT1A1 inducers may decrease raltegravir levels. Co-administration with aluminum and/or magnesium-containing antacids is not recommended. If co-administered with rifampin in adults, raltegravir dosing should be adjusted to 800 mg twice daily. Raltegravir is Pregnancy Category C. According to the product labeling, raltegravir should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.<sup>2</sup>

## Pharmacokinetics of Raltegravir in Pregnancy

### *Raltegravir Exposure in Pregnant Women*

Pharmacokinetic data related to the use of raltegravir in pregnancy is limited. A multicenter, open-label, phase IV study included HIV-infected pregnant adult women receiving ART including raltegravir 400 mg by mouth twice daily for at least two weeks before the pharmacokinetic analysis occurred. The exposure to

raltegravir, which was expressed as an area under the plasma concentration-time curve (AUC) at 12 hours, was lower during the third trimester compared to postpartum by 29%. The maximum concentration ( $C_{max}$ ) and concentration at 12 hours after raltegravir administration ( $C_{12}$ ) were also lower during the third trimester compared to postpartum by 18% and 36%, respectively. Out of a total of 22 patients, 86% achieved a VL less than 50 copies/mL near the time of delivery, and none of the newborns were infected with HIV. Overall, the study demonstrated highly variable pharmacokinetics of raltegravir during the third trimester of pregnancy.<sup>3</sup> The International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) 1026s was a multicenter, prospective study that also demonstrated highly variable pharmacokinetics of raltegravir during pregnancy. The AUC at 12 hours was lower in the second (6.6  $\mu\text{g}^*\text{hr}/\text{mL}$ ,  $p=0.03$ ) and third (5.4  $\mu\text{g}^*\text{hr}/\text{mL}$ ,  $p=0.001$ ) trimesters compared to postpartum (11.6  $\mu\text{g}^*\text{hr}/\text{mL}$ ). During the second trimester, 69% ( $n=11/16$ ) of the patients achieved a trough concentration above the target (raltegravir concentration at 12 hours [ $C_{12}$ ] greater than 0.035  $\mu\text{g}/\text{mL}$ ). There were 80% ( $n=33/41$ ) of the patients during the third trimester and 79% ( $n=30/38$ ) during the postpartum who had the trough concentration greater than the target. Almost all patients (92%) had a VL less than 400 copies/mL at the time of delivery, and none of the newborns were infected with HIV.<sup>4</sup> Croci, et al. reported a pregnant woman on raltegravir 400 mg by mouth twice daily achieving appropriate concentration of the drug (9.59  $\mu\text{g}/\text{mL}$ ) during the third trimester (target trough concentration greater than or equal to 1  $\mu\text{g}/\text{mL}$ ). This case report also indicated that raltegravir easily crossed the placenta as the concentration of raltegravir was the same between the umbilical cord and maternal plasma (both 0.19  $\mu\text{g}/\text{mL}$ ) at the time of delivery.<sup>5</sup>

### *Raltegravir Exposure in Newborns*

IMPAACT P1097, a multicenter study on raltegravir pharmacokinetics in neonates exposed to the drug during pregnancy, found that raltegravir easily crossed the placenta. Drug elimination rate was highly variable among neonates. The study suggested that the delayed elimination of raltegravir might be attributed to underdeveloped UGT1A1 activity and enterohepatic recirculation.<sup>6</sup> Clavel-Osorio, et al. reported a case of a premature newborn that was exposed to raltegravir through the mother also showed that raltegravir readily crossed the placenta. The mother was treatment-naïve and started on ART at 30 weeks gestation. Three doses of raltegravir 400 mg by mouth twice daily were administered before the Cesarean section. At one month of age, the premature newborn had a concentration of raltegravir that was 29 ng/mL, which was greater than the 95% inhibitory concentration of the drug (15 ng/mL).<sup>7</sup>

## Clinical Evidence of Raltegravir in Pregnancy

Most available data on the use of raltegravir in pregnancy are from case reports or retrospective studies. There are some cases of treatment-naïve, pregnant women with recently diagnosed HIV infection who started on ART including raltegravir late in pregnancy. Hegazi, et al. presented a case report of a 28-year-old female with

acute seroconversion at 28 weeks of pregnancy. CD4 count was 200 cells/ $\mu$ L and VL was  $1.74 \times 10^7$  copies/mL. ART with the addition of raltegravir was initiated. After 71 days of ART and at 39 weeks gestation, the patient's VL was 208 copies/mL. Following Caesarean section, HIV PCR tests were negative in the infant at birth and 18 months. This case report demonstrated a 4.9 log drop in VL within 10 weeks of ART initiation including raltegravir.<sup>8</sup> De Hoffer, et al. reported a case of a pregnant woman who received lamivudine/zidovudine 300/600 mg by mouth twice daily, lopinavir/ritonavir 400/200 mg by mouth twice daily, and raltegravir 400 mg by mouth twice daily immediately after she was diagnosed with HIV infection at 35 weeks of gestation. She delivered 19 days after starting ART via Cesarian section, and her VL was 20 copies/mL at the time of delivery. Zidovudine was given to the mother during delivery and to the newborn for 6 weeks. The newborn had an undetectable VL at birth and at one month.<sup>9</sup> Renet, et al. described a 34-year-old HIV-infected, treatment-naïve woman initiated on ART including zidovudine/lamivudine 300/150 mg one tablet by mouth twice daily and lopinavir/ritonavir 200/50 mg two tablets by mouth twice daily at 35 weeks of pregnancy. Following addition of raltegravir a week after starting ART, VL reduced from 523,975 to 1,163 copies/mL within 11 days of treatment. A 23-fold increase in serum alanine aminotransferase and 10-fold increase in serum aspartate aminotransferase were observed. Following discontinuation of raltegravir, serum transaminase levels returned to normal. The newborn was negative for HIV at one and two weeks and at one, two, and five months.<sup>10</sup> In a case series of four treatment-naïve women presenting as HIV positive in late pregnancy, Westling, et al. described outcomes following initiation

of ART plus raltegravir. Initial mean VL was 217,000 copies/mL (range 65,000–637,000 copies/mL). One of four patients reached an undetectable VL (less than 20 copies/mL) before delivery. For the remaining three patients, mean VL decline per week was 1.12 log. No adverse events in mother or child were reported. One mother received ART for only 8 days prior to delivery. All infants were confirmed HIV negative.<sup>11</sup>

There are case reports and retrospective studies on the use of raltegravir in HIV-infected, treatment-experienced pregnant women as well. Cha, et al. reported a 30-year-old, HIV-infected, treatment-experienced woman with VL of 106,110 copies/mL at week 33 of pregnancy on zidovudine/lamivudine and lopinavir/ritonavir. Raltegravir was added to the regimen with the intent to rapidly decrease VL before the Cesarean section at week 38. After four weeks of treatment with raltegravir, the patient's VL decreased to 200 copies/mL, which was a  $2.7 \log_{10}$  reduction. HIV PCR tests for the infant at birth, 2 weeks, 4 weeks, 2 months, and 4 months were negative.<sup>12</sup> Adeyemo, et al. reported three HIV-infected, treatment-experienced pregnant women who were admitted to the hospital at 38 weeks gestation and had VLs of 5,745 copies/mL, 37,843 copies/mL, and 28,364 copies/mL, respectively. Raltegravir and enfurvitide were added to their outpatient ART. One of the women had tenofovir added to the regimen as well. By day 11 of ART that included raltegravir, VLs reduced by approximately 2 logs. The newborns were HIV negative 12 weeks after the delivery.<sup>13</sup>

A retrospective, observational study by van Halsema, et al. assessed HIV-infected patients who received more than one dose of



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raltegravir, which included 6 pregnant HIV-infected, treatment-experienced women. The women were on raltegravir due to intolerance to a protease inhibitor (PI)-based therapy or to intensify their current PI-based regimen. Raltegravir was started at a median of 32 weeks gestation. All patients had an undetectable VL at the time of delivery and the newborns were HIV negative.<sup>14</sup> A retrospective chart review by Shust, et al. assessed a total of 8 pregnancies in 7 HIV-infected patients who failed the standard ART and put on a salvage therapy, which was defined as the use of darunavir, etravirine, raltegravir, or enfuvirtide for more than 7 days during pregnancy. The salvage therapy included raltegravir in 7 out of 8 pregnancies. VL decreased to below 1,000 copies/mL at the time of delivery in 7 out of 8 pregnancies. All newborns were HIV negative.<sup>15</sup> Pinnelli, et al. presented a case of a HIV-infected, treatment-experienced woman co-infected with hepatitis C virus initiated on raltegravir at 38 weeks of pregnancy. After 9 days of raltegravir use, HIV VL decreased from 75,584 to 260 copies/mL at delivery. No adverse events were reported, and the HIV PCR tests for the infant were negative at birth and at one month.<sup>16</sup>

There are three case series that reported the use of raltegravir in a group of HIV-infected, treatment-naïve and experienced pregnant women. Nobrega, et al. presented a case series of 14 HIV-infected pregnant women treated with raltegravir-containing ART. Nine patients were treatment-naïve and five were treatment-experienced with exposure to a PI. All patients were raltegravir-naïve. The ART consisted of raltegravir plus at least two other antiretroviral agents. The median gestational age was 36 weeks (range 34–38 weeks); mean CD4 cell count 338 cells/mL (range 65–1,203 cells/mL); median maternal VL 35,364 copies/mL (range 959–391,535 copies/mL); median exposure time to raltegravir 17 days (range 7–32 days); and median maternal VL decay 2.6 log. At delivery, 7 women had an undetectable VL (less than 50 copies/mL), four women had less than 500 copies/mL, and three did not have VL measurements. For these three women, one had an undetectable VL two weeks after delivery, one had VL of 266 copies/mL after three weeks, and one had VL of 89 copies/mL one week after delivery. All but one infant's VL was undetectable at one and three months. One HIV mother-to-child transmission likely due to in utero transmission was detected. No adverse events associated with the use of raltegravir were reported.<sup>17</sup> Taylor, et al. presented a case series of five HIV-infected women who were initiated on raltegravir in late pregnancy. Among these five patients, one patient was treatment-naïve and four were treatment-experienced. All patients were raltegravir-naïve. Mean exposure to raltegravir was 23 days (range 17–46 days) prior to delivery. Two of five patients had persistently low viremia and reached an undetectable VL prior to delivery. The remaining women experienced rapid VL suppression. Only one patient experienced transient increase in transaminases that resolved spontaneously during the first two weeks of raltegravir treatment. All five infants were HIV-negative.<sup>18</sup> Boucoiran, et al. reported a case series that included 11 HIV-infected pregnant women who began receiving raltegravir along with two or more antiretroviral agents at a median of 35.7 weeks gestation. Six patients were treatment-naïve and five were treatment-experienced. The patients received raltegravir for a median of 20 days. Overall, 81.8% (n=9/11) of the patients had VL less than 1,000 copies/mL at the time of delivery. Among these patients, 7 patients had an undetectable VL (less than 50 copies/mL). The newborns were HIV negative.<sup>19</sup>

There were two case series that reported the exposure of raltegravir to the infants born to HIV-infected women. McKeown, et al. described three cases of raltegravir use in late pregnancy in treatment-experienced women with multidrug resistant HIV. Neonate raltegravir concentrations were approximately 7 and 9.5 times higher than in the mothers' paired samples in patients 1 and 2, respectively. Although paired samples were not collected for the third patient, neonatal raltegravir concentration was high for 2.5 hours after delivery. Rapid maternal VL suppression was achieved with the addition of raltegravir. All three infants were HIV negative.<sup>20</sup> Hegazi, et al. described three cases of raltegravir used to prevent mother-to-child transmission of HIV in premature delivery. Raltegravir plasma concentrations were evaluated in mother and child before and after delivery. In two cases, raltegravir was initiated 22.5 and 14 hours prior to delivery. In one case, raltegravir was initiated at 22 weeks gestation. Raltegravir plasma concentrations were therapeutic in all three cases, including both mothers and infants. All three infants had negative HIV PCR test results and experienced no adverse reactions.<sup>21</sup>

### Guideline Recommendations

According to the guidelines developed by the United States Department of Health and Human Services, all HIV-infected pregnant women are recommended to receive ART regardless of CD4 count and VL to prevent the transmission of the virus to the newborn. All preferred regimens for treatment-naïve pregnant women include a backbone of two nucleoside reverse transcriptase inhibitors (NRTIs) such as abacavir/lamivudine, tenofovir/emtricitabine, tenofovir/lamivudine, or zidovudine/lamivudine. A recommended PI-based regimen includes atazanavir/ritonavir or darunavir/ritonavir in combination with two NRTIs. A recommended non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimen includes efavirenz with two NRTIs. However, this regimen is only recommended after the first 8 weeks of pregnancy. A recommended INSTI-based regimen is raltegravir in combination with two NRTIs.<sup>1</sup>

### Conclusion

A limited number of evidence on the use of raltegravir during pregnancy suggests that the drug is safe and effective in rapidly reducing the VL to prevent perinatal transmission of HIV. More pharmacokinetic and clinical studies are required to delineate the role of raltegravir in pregnant women. Pharmacists play a critical role in improving medication adherence in the HIV-infected patients. Also, pharmacists should be familiar with treatment options in HIV-infected pregnant women.

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**146<sup>th</sup> Annual Meeting  
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October 28 – 30, 2016



# NJPhA 2016 Award Nominations

## Award Name

Rosario J. Mannino Award

Bowl of Hygeia  
by APhA Foundation  
and NASPA

Andrew J. Preston Political  
Action Award

Donald J. Wernick Academic  
Achievement Award

Frederick B. Kilmer Award

NASPA Excellence in Innovation Award  
Sponsored by Upsher-Smith

Jesse Gaynor Award

Mortar & Pestle Award

William H. McNeill Award

Pharmacist Mutual Distinguished  
Young Pharmacist Award

Pharmaceutical Industry Award

## Award Description

This award honors President-Emeritus Rosario J. Mannino, and is given for meritorious service to the profession of pharmacy and the New Jersey Pharmacists Association.

Sponsored by National Alliance of State Pharmacy Associations (NASPA), the Bowl of Hygeia award is given to a living, NJ licensed pharmacist who has compiled an outstanding record of community service that, apart from the practice of pharmacy, reflects well on the profession.

Sponsored by past President and PAC Chairman Andrew J. Preston, this award is presented to the NJPhA member exhibiting outstanding effort in the political arena to benefit the profession and our patients.

Presented to an academician who has best served the profession and NJPhA. This recognition is presented to a pharmacist in academia who has also performed outstanding service for our profession at large.

Dr. Kilmer, a former NJPhA president, established the concept of research at J&J that became a standard for much of the pharmaceutical industry. He was a prodigious writer who valued articulate writing as a means of improving the pharmacy profession and the health of our citizenry.

Dr. Kilmer bequeathed a monetary gift to NJPhA to support a prize for the recognition of excellence in pharmacy writing by a member. All members, with the exception of educators and laboratory workers, are eligible. The award has been given since 1938 at the Association's annual convention.

Sponsored by NASPA, a nominee should be a practicing pharmacist within the geographic area represented by the presenting association and should have demonstrated innovative pharmacy practice resulting in improved patient care.

Presented to a consultant pharmacist who has shown meritorious service and dedication to the practice of pharmacy.

Authorized by the Board of Trustees, the Mortar & Pestle Award is given to an individual who is not a pharmacist, but who by virtue of his or her activity, has contributed to the profession of pharmacy and the public at large.

This award recognizes outstanding community service work by an NJPhA member for work done in the preceding year or years.

Presented to an outstanding pharmacist who has worked for the profession of pharmacy and who graduated in the past ten years.

This award is presented to a pharmacist who best meets the following guidelines:

- Degree in Pharmacy received within the last 10 years (2006 graduate or later)
- Licensed and in good standing to practice in New Jersey
- Current membership and participation in NJPhA
- Participation in national pharmacy associations, professional programs, and/or community service

Presented to a representative of the pharmaceutical industry who has advanced the profession through educational efforts or support to the profession

Independent Pharmacist of the Year Award	Presented to a practicing pharmacist who has demonstrated exemplary service to his/her patients and the community. Sponsored by Buy-sellapharmacy.com.
Cardinal Health Generation Rx Champions Award	Presented to a pharmacist in recognition of efforts to prevent prescription drug abuse and outstanding service to the pharmacy community to raise awareness of this serious public health problem.
Sidney B. Gilman Pharmacy Technician Award	Presented to an NJPhA Pharmacy Technician member in recognition of individual excellence and outstanding service to the pharmacy profession.

## How to nominate

Select the appropriate award from the list above, complete the online form below, and click SUBMIT. Several worthy candidates are nominated annually for each award, so please include as much supporting information as is appropriate.

### Instructions

- All fields must be completed legibly; incomplete nominations will not be considered
- Only nominations submitted on this form will be considered
- Only one nomination per form (to nominate the same person for multiple awards, you must complete multiple forms)

### Nominator Info:

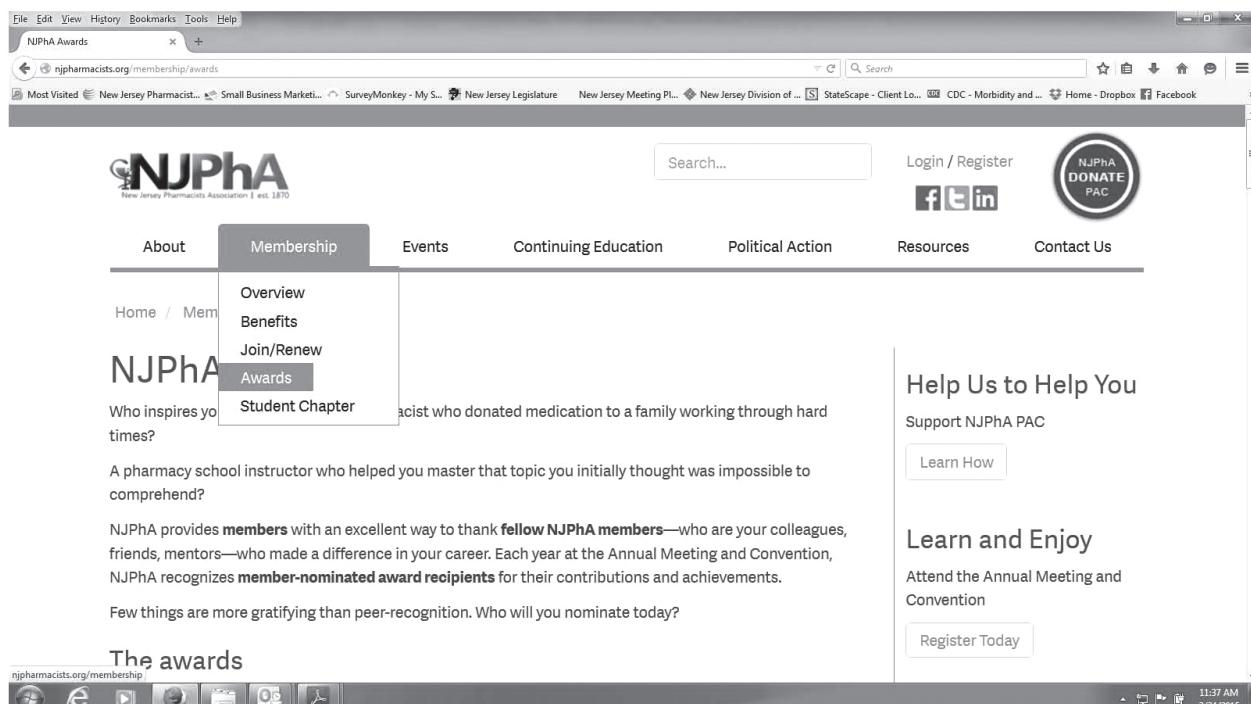
- Nominator name
- Nominator phone
- Nominator email

### Nominee Info:

- Award name
- Nominee name
- Nominee phone
- Nominee email

### Nominee title

- Tell us why the candidate should receive this award
- Supporting material



The screenshot shows a computer browser window displaying the NJPhA website at [njpharmacists.org/membership/awards](http://njpharmacists.org/membership/awards). The page header includes the NJPhA logo and navigation links for About, Membership, Events, Continuing Education, Political Action, Resources, and Contact Us. The Membership menu is currently active, showing options like Overview, Benefits, Join/Renew, Awards (which is highlighted), and Student Chapter. A sidebar on the right features sections for "Help Us to Help You" (with a "Learn How" button) and "Learn and Enjoy" (with a "Register Today" button). The main content area contains text about the awards program and a call to action for peer nomination.

[www.njpharmacists.org/membership/awards](http://www.njpharmacists.org/membership/awards)

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