Drug Topics® SEPTEMBER 2013 CE: MTM CONSIDERATIONS IN OSTEOPOROSIS CARE • OTC: HAIR AND SCALP VOL. 157 NO. 9

IMMUNIZATION CLAIMS
How to submit winners 32

COMPOUNDER LAWSUIT
Insurer denies adult Rx coverage 53

New Drug Review
OSPEMIFENE
FOR DYSPAREUNIA PAGE 40

Drug Topics®

VOL. 157 NO. 9
Voice of the Pharmacist
DrugTopics.com
September 2013

Patient-Centered Medical Home

YOUR ROLE WILL GROW as PCMH model evolves

PAGE 36

CPE CREDIT: 2.0 ACPE

MTM considerations in osteoporosis care: Part 1 Page 42

Earn CE credit for this activity at DrugTopics.com/cpe

ADVANSTAR MEDICAL COMMUNICATIONS GROUP

facebook.com/DrugTopics
twitter.com/Drug_Topics

Boehringer Ingelheim
Roxane Laboratories

Roxane Laboratories

Your Connection to Quality™

At Roxane Laboratories, we work for the well-being of every customer and patient. That means you can always expect the highest quality in our products, in our customer service and in our commitment to research. This pursuit of quality defines our focus. Every Roxane product carries the combined expertise and strength of our entire team. Roxane is your connection to quality generic pharmaceuticals.

Roxane. Right Now.™

QUALITY	GROWTH	AFFORDABLITY	INNOVATION

roxane.com

Drug Topics®

Editorial Mission: *Drug Topics*, a monthly news magazine guided by an editorial advisory board of pharmacy experts, reports on all phases of community, retail, and health-system issues and trends. We offer a forum for pharmacists to share practical ideas for better pharmacy management and patient care.

CONTENT

CONTENT CHANNEL DIRECTOR Julia Talsma
(440) 891-2792 / jtalsma@advanstar.com

CONTENT CHANNEL MANAGER Julianne Stein
(440) 826-2834 / jstein@advanstar.com

CONTENT EDITOR Mark Lowery
(440) 891-2705 / mlowery@advanstar.com

DIGITAL & INTERACTIVE CONTENT MANAGER Brandon Glenn
(440) 891-2638 / bglenn@advanstar.com

CONTENT COORDINATOR Miranda Hester

GROUP ART DIRECTOR Robert McGarr

ART DIRECTOR Nicole Davis

PUBLISHING AND SALES

EXECUTIVE VICE PRESIDENT Georgiann DeCenzo
(440) 891-2778 / gdecenzo@advanstar.com

VICE PRESIDENT, GROUP PUBLISHER Ken Sylvia
(732) 346-3017 / ksylvia@advanstar.com

GROUP PUBLISHER Mike Weiss
(732) 346-3071 / mweiss@advanstar.com

NATIONAL ACCOUNT MANAGER Sharon Ames
(732) 346-3033 / sames@advanstar.com

NATIONAL ACCOUNT MANAGER Mark Hildebrand
732-346-3006 / mhildebrand@advanstar.com

ACCOUNT MANAGER, CLASSIFIED/ DISPLAY ADVERTISING Darlene Balzano
(440) 891-2779 / dbalzano@advanstar.com

ACCOUNT MANAGER, RECRUITMENT ADVERTISING Joanna Shippoli
440-891-2615 / jshippoli@advanstar.com

BUSINESS DIRECTOR, EMEDIA Don Berman
(212) 951-6745 / dberman@advanstar.com

DIRECTOR, SALES DATA Gail Kaye
(732) 346-3042 / gkaye@advanstar.com

SALES SUPPORT Hannah Curis
(732) 346-3055 / hcuris@advanstar.com

REPRINT SERVICES
877-652-5295, ext. 121 / bkolb@wrightsmedia.com
Outside US, UK, direct dial: 281-419-5725, Ext. 121

LIST ACCOUNT EXECUTIVE Tamara Phillips
(440) 891-2773 / tphillips@advanstar.com

PERMISSIONS Maureen Cannon
(440) 891-2742 or (800) 225-4569 ext. 2742
Fax: (440) 891-2650 / mcannon@advanstar.com

PRODUCTION

SENIOR PRODUCTION MANAGER Karen Lenzen
(218) 740-6371 / klenzen@media.advanstar.com

AUDIENCE DEVELOPMENT

CORPORATE DIRECTOR Joy Puzzo
(440) 319-9570 / jpuzzo@advanstar.com

DIRECTOR Christine Shappell
(201) 391-2359 / cshappell@advanstar.com

MANAGER Joe Martin
(218) 740-6375 / jmartin@advanstar.com

CIRCULATION

SUBSCRIPTION CUSTOMER SERVICE/ADDRESS CHANGES
(888) 527-7008 / magazines@superfill.com
PO Box 6079, Duluth, MN 55806-6079, USA

CONTACT US

24950 COUNTRY CLUB BLVD., SUITE 200
NORTH OLMSTED, OHIO 44070
MAIN NUMBER: (440) 243-8100
MAIN FAX NUMBER: (440) 891-2735
CUSTOMER SERVICE: (877) 922-2022
EMAIL: DRUGTOPICS@ADVANSTAR.COM

ADVANSTAR

Joe Loggia
CHIEF EXECUTIVE OFFICER

Tom Florio
CHIEF EXECUTIVE OFFICER FASHION GROUP, EXECUTIVE VICE-PRESIDENT

Tom Ehardt
EXECUTIVE VICE-PRESIDENT, CHIEF ADMINISTRATIVE OFFICER & CHIEF FINANCIAL OFFICER

Georgiann DeCenzo
EXECUTIVE VICE-PRESIDENT

Chris DeMoulin
EXECUTIVE VICE-PRESIDENT

Ron Wall
EXECUTIVE VICE-PRESIDENT

Rebecca Evangelou
EXECUTIVE VICE-PRESIDENT, BUSINESS SYSTEMS

Tracy Harris
SR VICE-PRESIDENT

Francis Heid
VICE-PRESIDENT, MEDIA OPERATIONS

Michael Bernstein
VICE-PRESIDENT, LEGAL

J Vaughn
VICE-PRESIDENT, ELECTRONIC INFORMATION TECHNOLOGY

CONTENTS

SEPTEMBER 2013

Drug Topics®
Voice of the Pharmacist
DrugTopics.com

VOL. 157 NO. 9

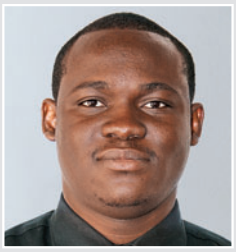
COVER STORY

Patient-Centered Medical Home

Team-based coordination of care provides patients with comprehensive, integrated, efficient, and effective primary healthcare. The question for pharmacists: Are we there yet? PAGE 36

PRESCRIBED READING

Jill Fitzgerald, PharmD
New CPE is on the way PAGE 6



Tolulope Alabi, PharmD Cand.
The menthol conspiracy PAGE 7

Jean Moon, PharmD
The ABCs of PCMH PAGE 36

Kathryn Wheeler, PharmD
New SERM approved PAGE 40

Ned Milenkovich, PharmD
Compounders vs. insurer PAGE 53

THINKSTOCK/ISTOCKPHOTO

30 years of serving the healthcare community

Advanced sterile manufacturing capabilities

IN² VIGORATION

Extensive portfolio of products and dosages

Leader in liquid and semi-solid generics, ophthalmics and otics

Experience is a wonderful thing. Having 30 years of it not only makes you more accomplished, it gives you a track record — such as being the leader in liquid and semi-solid generics. But experience is nothing without energy. The energy to turn ideas into accomplishments — which include sterile manufacturing expertise, producing a variety of medications in unique dosages, creating proprietary machinery that delivers enhanced efficiency and production capacity, and increasing our financial commitment to R&D. After 30 years, Hi-Tech Pharmacal is still an aggressive, youthful company poised for even greater growth in the years to come. And for our strategic partners, that's invigorating. To learn more visit **hitechpharm.com** or call **800.262.9010**.

Scan for more information.

800.262.9010 | hitechpharm.com

Hi-Tech PHARMACAL Co Inc.

September 2013 **Drug Topics** Voice of the Pharmacist Vol. 157 No. 9

CPE **CONTINUING EDUCATION**

MTM considerations in osteoporosis

As the U.S. population ages, osteoporosis cases are on the rise. The pharmacist may be the first healthcare provider to identify a patient – and is certainly the best one to provide MTM. **PAGE 42**

What's happening now at DrugTopics.com

SOCIAL MEDIA

JOIN US ONLINE!
Read the latest breaking news and give us your feedback!

facebook.com/DrugTopics

twitter.com/Drug_Topics

DT BLOG

Time to let go
A cutting-edge calculator that cost Goose Rawlings half a semester's tuition back in '73 sits in a drawer, replaced by a $20 solar-powered wonder gizmo. Sometimes, no matter what the investment, you just have to move on. *www.drugtopics.com*.

WEB EXCLUSIVES

Video: Secure drug supply chain
http://drugtopics.com/securechain

Guide to robbery prevention
http://drugtopics.com/robprevent

Mail-order praised in DOD audit
http://drugtopics.com/DODaudit

DIGITAL EDITION

Subscribe to the monthly digital edition of *Drug Topics* and receive the journal electronically with live links. Go to http://drugtopics.com/digital.

Drug Topics (ISSN# 0012-6616) is published monthly and Drug Topics Digital Edition (ISSN# 1937-8157) is issued every week by Advanstar Communications, Inc., 131 West First St., Duluth, MN 55806-2065. One-year subscription rates: $61 in the United States & Possessions; $109 in Canada and Mexico; all other countries, $109. Single copies (prepaid only) $10 in the United States; $10 in Canada and Mexico; all other countries, $15. Include $6 per copy for U.S. postage and handling. **Periodicals postage paid** at Duluth, MN 55806 and additional mailing offices. **POSTMASTER:** Please send address changes to Drug Topics, P.O. Box 6079, Duluth, MN 55806-6079. Canadian G.S.T. number: R-124213133RT001. Publications Mail Agreement Number 40612608. Return undeliverable Canadian addresses to: IMEX Global Solutions PO Box 25542 London, ON N6C 6B2 CANADA. Printed in the U.S.A.

IMAGE: THINKSTOCK / ISTOCKPHOTO

No other BTC product relieves more cold and sinus symptoms

The only behind-the-counter (BTC) cold and sinus liquid gel that delivers pseudoephedrine with a pain reliever, cough suppressant, and antihistamine.

BAYER

150 Years
Science For A
Better Life

DISPENSED AS WRITTEN Jill Fitzgerald, PharmD

Continuing professional development opportunities

Thank you to those of you who are completing and enjoying our ongoing continuing pharmacy education offerings through *Drug Topics*. Last month completed the series on Pain Management and this month begins the first of two mini-sessions.

This month and next, the focus is on the considerations for osteoporosis prevention and management in medication therapy management (MTM). While MTM sessions are intended to identify, resolve, and prevent medication-related problems, patient health maintenance and disease prevention are also important components of MTM. Prevention and treatment of osteoporosis are major interventions that can prevent significant morbidity and mortality in our patients. Appropriate identification of patients at risk, recommendations for osteoporosis screenings, and management of preventative and maintenance therapies are all important aspects of the MTM function. We have designed the two monthly activities to assist you in considering recommendations for screening, prevention, treatment, and monitoring of patients who are at risk of or who have osteoporosis.

November and December's activities will focus on MTM considerations for patients with multiple sclerosis (MS). There have been many new, even oral, medications for multiple sclerosis over the past several years. While pharmacists are unlikely to recommend specific therapies for MS, there are related conditions for which the pharmacist might be involved from the standpoint of MTM. These two monthly installments will focus on drug-therapy options, adherence issues, and health-maintenance recommendations for the patient with MS.

Series success

In addition, we recognize that the diabetes series provided practical, user-friendly information on the treatment and monitoring of diabetes. The live meeting held in May 2013 was extremely successful, and feedback from the activities has been very positive.

One participant said this about the program as a whole: "The MTM event was AWESOME. I was a little nervous about being prepared, but the speakers and facilitators were excellent, supportive, and encouraging, which made me feel more comfortable. I am SO GLAD I participated in this series."

We have reserved Saturday, November 9, at the Lincoln Medical and Mental Health Center, Bronx, N.Y., for the next Diabetes MTM live event. For more information, go to *http://bit.ly/UCONNdm*.

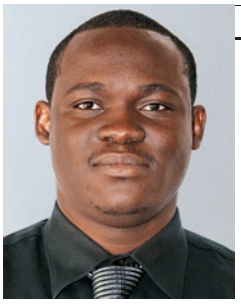
The month of January will also continue the theme of diabetes management. While the diabetes series addressed many of the drug therapies for diabetes, there have been several advances since the articles were published. January will focus on new therapies and changes in the diabetes guidelines.

Cardiometabolic Syndrome

We compiled your responses and tallied the needs of those who have been participating in our CE activities, and have decided that the next "big installment" will be a year-long discussion on MTM Considerations in the Patient with Cardiometabolic Syndrome. Beginning in February of 2014, topics will include hypertension, hyperlipidemia, anticoagulation, heart failure, weight loss, and smoking cessation, among others. As with the diabetes series, we plan to incorporate application-based learning through online interactive cases and practice-based learning through a live event and certification. This will be a comprehensive continuing professional development opportunity that you will not want to miss.

Please do not hesitate to provide us with feedback on any and all of our activities by e-mailing me at jill.fitzgerald@uconn.edu. We are committed to making your continuing pharmacy education a professional development experience by providing you with the tools to help your patients achieve better health outcomes through medication therapy management. DT

Jill Fitzgerald, PharmD, *is director of Pharmacy Professional Development and associate clinical professor at the University of Connecticut School of Pharmacy* (www.pharmacy.uconn.edu/academics/ce).



STUDENT CORNER Tolulope Alabi, PharmD/MPH Candidate 2014

Menthol cigarette ads tightly targeted

While serving my student pharmacist public health rotation, I researched tobacco use among African Americans in Solano County, California, along with the advertising tactics used by the tobacco industry to target them. What I learned was dismaying.

Health risks

The advertisement of mentholated cigarettes in African-American neighborhoods is incessant. The county reported that up to 23% of its population is made up of smokers, some of whom began smoking as early as the age of 12.

This issue is further complicated by the prevalence of other reported health risks: 21% of county residents are obese, 22% have hypertension, and 6.5% have diabetes. In Solano County, one in every five deaths is cigarette-related.

Marketing ploys

Although FDA has intervened to provide safety and protection on drug-related issues, little has been done regarding the use of cigarettes. While FDA did ban fruit- and candy-flavoring in cigarettes, tobacco companies have never diminished their efforts to ensnare as many tobacco users as possible.

One successful device to lure more young people into smoking cigarettes was the addition of menthol to cigarettes. And cigarette advertising is designed to target young adults and children in African-American communities.

Even though clinical research studies have disproved the claims for the benefits of mentholated cigarettes made by tobacco companies, this industry continually promotes such claims throughout the media. As a result, members of the American-African population commonly believe that menthol cigarettes have medicinal benefits and are less harmful than non-mentholated cigarettes.

The taste and sensation of menthol, which mask the taste of tobacco, are yet more devices the tobacco industry uses to prey on African-American youth.

Focused advertising

Further studies document the fact that African-American neighborhoods are targeted more than other communities with advertisements for leading brands of menthol cigarettes. Most alarming is that these advertisements are prominent near high schools. At convenience stores and gas stations in poorer neighborhoods, advertisements are strategically placed at eye level, such as on windows and at cash registers.

A recent study compared the ways cigarette advertisements are exposed to young people of different races. African-American youths recognized the Newport menthol-flavored cigarettes more than other racial groups did. This result was attributed to uncontrolled exposure of advertisements of this product throughout their communities. It is not surprising there is increased smoking initiated among young African Americans.

Local initiatives

To its credit, the Solano Board of Supervisors passed a resolution banning the sale of menthol cigarettes. In 2013, the Solano Tobacco Prevention and Education program and other local groups then signed a petition requesting a ban on menthol cigarettes and sent it to FDA.

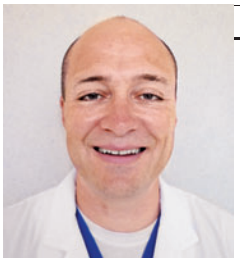
As pharmacists we are obligated to be concerned about the health issues of all the members of our community. One way to act on this concern is involvement in local tobacco prevention and education programs that promote a healthier style of living for all communities.

Another meaningful step would be to write to FDA. The more communications and petitions FDA receives regarding mentholated cigarettes, the greater the hope that the agency will take up this issue and eventually ban this health hazard. DT

References

1. Unger JB, Allen B Jr, Leonard E, et al. Menthol and non-menthol cigarette use among Black smokers in Southern California. *Nicotine Tob Res.* 2010 Apr;12(4):398-407. doi: 10.1093/ntr/ntq016. Epub 2010 Feb 18. *http://www.ncbi.nlm.nih.gov/pubmed/20167636.*
2. *Vallejo Times Herald*. Solano renews call for FDA to ban harmful menthol in cigarettes. 07/076/2013. *http://www.timesheraldonline.com/ci_23609868/solano-renews-call-fda-ban-harmful-menthol-cigarettes.*
3. Dauphinee AL, Doxey JR, Schleicher NC, et al. Racial differences in cigarette brand recognition and impact on youth smoking. *BMC Public Health*. 2013 Feb 25;13:170. doi: 10.1186/1471-2458-13-170. *http://www.ncbi.nlm.nih.gov/pubmed/23442215.*
4. Henriksen L, Schleicher NC, Dauphinee AL, Fortmann SP. Targeted advertising, promotion, and price for menthol cigarettes in California high school neighborhoods. *Nicotine Tob Res.* 2012 Jan;14(1):116-21. doi: 10.1093/ntr/ntr122. Epub 2011 Jun 24. *http://www.ncbi.nlm.nih.gov/pubmed/21705460.*

Tolulope Alabi *is a 2014 PharmD/MPH candidate at Touro University College of Pharmacy in Vallejo, Calif. Contact him at tolulope.alabi@tu.edu.*



IN MY VIEW Amy Holmes, PharmD; James L. Crecraft, RPh

Playing to strength: Pharmacists on the team

During college-bowl season, an online feature about North Carolina brothers Casey and Connor Barth, both placekickers, got us thinking about the practice of medicine and how it relates to teamwork in sporting events.

The entire multidisciplinary team can be compared to a football team. Our opponents are the many things we struggle with or fight against every day — disease, interruptions that distract us from important tasks, insurance companies — you can probably cite others from your own practice.

The lineup

The most obvious counterpart to the quarterback may be the physician. After all, both are leaders, heroes even, of their respective teams. Not all roles are as highly esteemed or as obviously necessary as the quarterback's, but we all know that the quarterback alone cannot carry a game. Other players for the offense include the nurses, CNAs, respiratory therapists, physical therapists, etc., who act as the running backs and wide receivers. They are essential players to have on the field to advance the ball toward the goal.

Pharmacists and pharmacy technicians may be more like the offensive line, performing unrecognized and less visible tasks. Also unacclaimed and overlooked are the members of the special teams. Pharmacists can certainly relate to these players who, like them, must attend training camp, practice, and games, with little opportunity for playing time. As Casey Barth, one of the placekicker brothers, recently said in an interview, "Sometimes they need you and sometimes they don't."[1]

Ups and downs

Studies clearly indicate the utility of the pharmacist as part of the patient-care team. Medical errors are reduced and outcomes improved by having pharmacists attend rounds in the intensive care unit as well as the general medicine floors.[2,3] However, in pharmacy, as in many other professions, there are good days and bad days, with most falling somewhere in between.

Pharmacists may participate in rounds during times of low census or low acuity and not have the opportunity to make significant interventions. Similarly, frontline pharmacists in order entry or dispensing positions may check hundreds of doses without finding any problems requiring their expert intervention. These periods of lull can lead to feelings of uselessness and idleness. It can be easy to forget significant interventions recently made or times that consultation was sought. During these lulls, pharmacists may begin to feel unnecessary and worry about earning their keep, so to speak.

Also like special team members, pharmacists can sometimes make the difference in a win or a loss. Catching those medication errors or preventing adverse drug reactions is like having a kicker come in on the last play to score the field goal that wins the game.

Don't forget the punt

The punter, another lesser-known player whose role it is to kick the ball away to the other team, is very important for field position. This brings to mind the role of pharmacists in antimicrobial stewardship. The impact of antimicrobial stewardship may not be effective right away, but it does have a positive impact globally on resistance patterns; it's like providing better field position against the hospital-wide antibiogram.

If you find yourself doubting your utility in your patient-care role, remember the loneliness of the special teams players and keep your eye on the ball. They may need you on the next play! DT

References

1. Brett Friedlander. Casey Barth doesn't get a kick out of unfulfilling UNC Pro Day. StarNews Online. March 26, 2013. *http://acc.blogs.starnewsonline.com/35972/casey-barth-doesnt-get-a-kick-out-of-unfulfilling-unc-pro-day/*
2. Leape LL, Cullen DJ, Clapp MD, et al. Pharmacist participation on physician rounds and adverse drug events in the intensive care unit. *JAMA.* 1999; 282(3):267-270.
3. Kucukarshan SN, Peters M, Mlynarek M, et al. Pharmacists on rounding teams reduce preventable adverse drug events in hospital general medicine units. *Arch Intern Med.* 2003; 163(17):2014-2018.

Amy Holmes *is a neonatal clinical pharmacy specialist for Novant Health Forsyth Medical Center in Winston Salem, N.C.*
James Crecraft *is a clinical staff pharmacist for Novant.*


Introducing a
NEW approach in
type 2 diabetes
treatment...

INVOKANA™ (canagliflozin) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

INVOKANA™ is not recommended in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- History of a serious hypersensitivity reaction to INVOKANA™.
- Severe renal impairment (eGFR <30 mL/min/1.73 m^2), end stage renal disease, or patients on dialysis.

WARNINGS and PRECAUTIONS

- **Hypotension:** INVOKANA™ causes intravascular volume contraction. Symptomatic hypotension can occur after initiating INVOKANA™, particularly in patients with impaired renal function (eGFR <60 mL/min/1.73 m^2), elderly patients, and patients on either diuretics or medications that interfere with the renin-angiotensin-aldosterone system (eg, angiotensin-converting-enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs]), or patients with low systolic blood pressure. Before initiating INVOKANA™ in patients with one or more of these characteristics, volume status should be assessed and corrected. Monitor for signs and symptoms after initiating therapy.

Please see additional Important Safety Information and Brief Summary of full Prescribing Information on the following pages.

NOW AVAILABLE

In adults with type 2 diabetes,

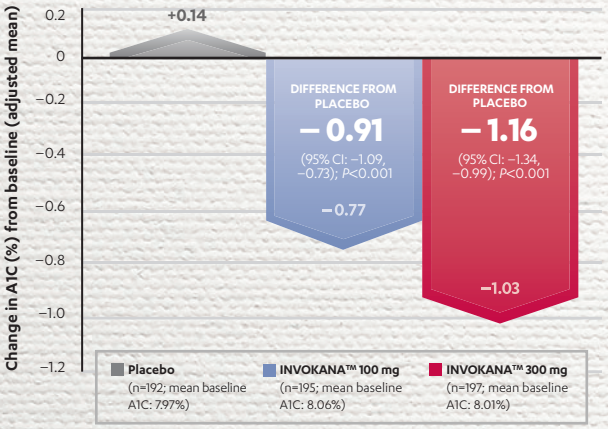
ENVISION NEW POSSIBILITIES

Introducing INVOKANA™—the first and only treatment option approved in the United States that reduces the reabsorption of glucose in the kidneys via sodium glucose co-transporter-2 (SGLT2) inhibition[1]

A1C Reductions as Monotherapy

INVOKANA™ monotherapy provided statistically significant A1C reductions vs placebo at 26 weeks[1]

A1C Change From Baseline With INVOKANA™ Monotherapy[1]



Effect on Weight*

Statistically significant weight reductions vs placebo at 26 weeks (*P*<0.001)[1]

>> Difference from placebo†:
100 mg: −2.2%; 300 mg: −3.3%

Impact on Systolic Blood Pressure (SBP)*

Statistically significant SBP lowering vs placebo at 26 weeks (*P*<0.001)[2]

>> Difference from placebo†:
100 mg: −3.7 mm Hg; 300 mg: −5.4 mm Hg

INVOKANA™ is not indicated for weight loss or as antihypertensive treatment.

***Prespecified secondary endpoint.**

†Adjusted mean.

A1C Reductions vs Sitagliptin

INVOKANA™ 300 mg demonstrated greater A1C reductions vs sitagliptin 100 mg, in combination with metformin + a sulfonylurea, at 52 weeks (*P*<0.05)[1]

>> Difference from sitagliptin†: −0.37%

Incidence of Hypoglycemia

Monotherapy over 26 weeks:
100 mg: 3.6%; 300 mg: 3.0%; placebo: 2.6%[1]

With metformin and a sulfonylurea over 52 weeks:
INVOKANA™ 300 mg: 43.2%; sitagliptin 100 mg: 40.7%[1]

>> Insulin and insulin secretagogues are known to cause hypoglycemia. INVOKANA™ can increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue

Convenient Once-Daily Dosing[1]

>> Recommended starting dose: INVOKANA™ 100 mg

>> Dose can be increased to 300 mg in patients tolerating 100 mg, who have an eGFR of ≥60 mL/min/1.73 m^2 and require additional glycemic control

The most common (≥5%) adverse reactions were female genital mycotic infection, urinary tract infection, and increased urination.

References: 1. Invokana [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals, Inc; 2013. **2.** Stenlöf K, Cefalu WT, Kim KA, et al. Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise. *Diabetes Obes Metab*. 2013;15(4):372-382.

Learn more at INVOKANAhcp.com/journal

Invokana™
canagliflozin tablets

IMPORTANT SAFETY INFORMATION *(continued from first page)*

WARNINGS and PRECAUTIONS *(cont'd)*

- **Impairment in Renal Function:** INVOKANA™ (canagliflozin) increases serum creatinine and decreases eGFR. Patients with hypovolemia may be more susceptible to these changes. Renal function abnormalities can occur after initiating INVOKANA™. More frequent renal function monitoring is recommended in patients with an eGFR below 60 mL/min/1.73 m^2.
- **Hyperkalemia:** INVOKANA™ can lead to hyperkalemia. Patients with moderate renal impairment who are taking medications that interfere with potassium excretion, such as potassium-sparing diuretics, or medications that interfere with the renin-angiotensin-aldosterone system are more likely to develop hyperkalemia. Monitor serum potassium levels periodically after initiating INVOKANA™ in patients with impaired renal function and in patients predisposed to hyperkalemia due to medications or other medical conditions.
- **Hypoglycemia With Concomitant Use With Insulin and Insulin Secretagogues:** Insulin and insulin secretagogues are known to cause hypoglycemia. INVOKANA™ can increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with INVOKANA™.
- **Genital Mycotic Infections:** INVOKANA™ increases the risk of genital mycotic infections. Patients with a history of genital mycotic infections and uncircumcised males were more likely to develop genital mycotic infections. Monitor and treat appropriately.
- **Hypersensitivity Reactions:** Hypersensitivity reactions (eg, generalized urticaria), some serious, were reported with INVOKANA™ treatment; these reactions generally occurred within hours to days after initiating INVOKANA™. If hypersensitivity reactions occur, discontinue use of INVOKANA™; treat per standard of care and monitor until signs and symptoms resolve.
- **Increases in Low-Density Lipoprotein (LDL-C):** Dose-related increases in LDL-C occur with INVOKANA™. Monitor LDL-C and treat per standard of care after initiating INVOKANA™.
- **Macrovascular Outcomes:** There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with INVOKANA™ or any other antidiabetic drug.

DRUG INTERACTIONS

- **UGT Enzyme Inducers:** Rifampin: Co-administration of canagliflozin with rifampin, a nonselective inducer of several UGT enzymes, including UGT1A9, UGT2B4, decreased canagliflozin area under the curve (AUC) by 51%. This decrease in exposure to canagliflozin may decrease efficacy. If an inducer of these UGTs (eg, rifampin, phenytoin, phenobarbitol, ritonavir) must be co-administered with INVOKANA™ (canagliflozin), consider increasing the dose to 300 mg once daily if patients are currently tolerating INVOKANA™ 100 mg once daily, have an eGFR greater than 60mL/min/1.73 m^2, and require additional glycemic control. Consider other antihyperglycemic therapy in patients with an eGFR of 45 to less than 60 mL/min/1.73 m^2 receiving concurrent therapy with a UGT inducer and requiring additional glycemic control.
- **Digoxin:** There was an increase in the area AUC and mean peak drug concentration (C_{max}) of digoxin (20% and 36%, respectively) when co-administered with INVOKANA™ 300 mg. Patients taking INVOKANA™ with concomitant digoxin should be monitored appropriately.

USE IN SPECIFIC POPULATIONS

- **Pregnancy Category C:** There are no adequate and well-controlled studies of INVOKANA™ in pregnant women. Based on results from rat studies, canagliflozin may affect renal development and maturation. In a juvenile rat study, increased kidney weights and renal pelvic and tubular dilatation were evident at ≥0.5 times clinical exposure from a 300-mg dose.

  These outcomes occurred with drug exposure during periods of animal development that correspond to the late second and third trimester of human development. During pregnancy, consider appropriate alternative therapies, especially during the second and third trimesters. INVOKANA™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
- **Nursing Mothers:** It is not known if INVOKANA™ is excreted in human milk. INVOKANA™ is secreted in the milk of lactating rats, reaching levels 1.4 times higher than that in maternal plasma. Data in juvenile rats directly exposed to INVOKANA™ showed risk to the developing kidney (renal pelvic and tubular dilatations) during maturation. Since human kidney maturation occurs in utero and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing

human kidney. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from INVOKANA™, a decision should be made whether to discontinue nursing or to discontinue INVOKANA™, taking into account the importance of the drug to the mother.

- **Pediatric Use:** Safety and effectiveness of INVOKANA™ in pediatric patients under 18 years of age have not been established.
- **Geriatric Use:** Two thousand thirty-four (2034) patients 65 years and older, and 345 patients 75 years and older were exposed to INVOKANA™ in nine clinical studies of INVOKANA™. Patients 65 years and older had a higher incidence of adverse reactions related to reduced intravascular volume with INVOKANA™ (such as hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration), particularly with the 300-mg daily dose, compared to younger patients; more prominent increase in the incidence was seen in patients who were ≥75 years of age. Smaller reductions in HbA1C with INVOKANA™ relative to placebo were seen in older (65 years and older; -0.61% with INVOKANA™ 100 mg and -0.74% with INVOKANA™ 300 mg relative to placebo) compared to younger patients (-0.72% with INVOKANA™ 100 mg and -0.87% with INVOKANA™ 300 mg relative to placebo).
- **Renal Impairment:** The efficacy and safety of INVOKANA™ were evaluated in a study that included patients with moderate renal impairment (eGFR 30 to <50 mL/min/1.73 m^2). These patients had less overall glycemic efficacy and had a higher occurrence of adverse reactions related to reduced intravascular volume, renal-related adverse reactions, and decreases in eGFR compared to patients with mild renal impairment or normal renal function (eGFR ≥60 mL/min/1.73 m^2); patients treated with INVOKANA™ 300 mg were more likely to experience increases in potassium.

  The efficacy and safety of INVOKANA™ have not been established in patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2), with end-stage renal disease (ESRD), or receiving dialysis. INVOKANA™ is not expected to be effective in these patient populations.
- **Hepatic Impairment:** No dosage adjustment is necessary in patients with mild or moderate hepatic impairment. The use of INVOKANA™ has not been studied in patients with severe hepatic impairment and it is therefore not recommended.

OVERDOSAGE

- There were no reports of overdose during the clinical development program of INVOKANA™ (canagliflozin).

  In the event of an overdose, contact the Poison Control Center. It is also reasonable to employ the usual supportive measures, eg, remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment as dictated by the patient's clinical status. Canagliflozin was negligibly removed during a 4-hour hemodialysis session. Canagliflozin is not expected to be dialyzable by peritoneal dialysis.

ADVERSE REACTIONS

- The most common (≥5%) adverse reactions were female genital mycotic infections, urinary tract infections, and increased urination. Adverse reactions in ≥2% of patients were male genital mycotic infections, vulvovaginal pruritis, thirst, nausea, and constipation.

K02CAN13149

Please see Brief Summary of full Prescribing Information on the following pages.

Invokana™
canagliflozin tablets

Janssen
PHARMACEUTICAL COMPANIES OF Johnson&Johnson

Janssen Pharmaceuticals, Inc.

Canagliflozin is licensed from Mitsubishi Tanabe Pharma Corporation.

April 2013 K02CAN13075

INVOKANA™

(canagliflozin) tablets, for oral use

Brief Summary of Prescribing Information.

INDICATIONS AND USAGE

INVOKANA™ (canagliflozin) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus *[see Clinical Studies (14) in full Prescribing Information]*.

Limitation of Use: INVOKANA is not recommended in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

CONTRAINDICATIONS

- History of a serious hypersensitivity reaction to INVOKANA *[see Warnings and Precautions]*.
- Severe renal impairment (eGFR less than 30 mL/min/1.73 m^2), end stage renal disease or patients on dialysis *[see Warnings and Precautions and Use in Specific Populations]*.

WARNINGS AND PRECAUTIONS

Hypotension: INVOKANA causes intravascular volume contraction. Symptomatic hypotension can occur after initiating INVOKANA *[see Adverse Reactions]* particularly in patients with impaired renal function (eGFR less than 60 mL/min/1.73 m^2), elderly patients, patients on either diuretics or medications that interfere with the renin-angiotensin-aldosterone system (e.g., angiotensin-converting-enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs]), or patients with low systolic blood pressure. Before initiating INVOKANA in patients with one or more of these characteristics, volume status should be assessed and corrected. Monitor for signs and symptoms after initiating therapy.

Impairment in Renal Function: INVOKANA increases serum creatinine and decreases eGFR. Patients with hypovolemia may be more susceptible to these changes. Renal function abnormalities can occur after initiating INVOKANA *[see Adverse Reactions]*. More frequent renal function monitoring is recommended in patients with an eGFR below 60 mL/min/1.73 m^2.

Hyperkalemia: INVOKANA can lead to hyperkalemia. Patients with moderate renal impairment who are taking medications that interfere with potassium excretion, such as potassium-sparing diuretics, or medications that interfere with the renin-angiotensin-aldosterone system are more likely to develop hyperkalemia *[see Adverse Reactions]*.

Monitor serum potassium levels periodically after initiating INVOKANA in patients with impaired renal function and in patients predisposed to hyperkalemia due to medications or other medical conditions.

Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues: Insulin and insulin secretagogues are known to cause hypoglycemia. INVOKANA can increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue *[see Adverse Reactions]*. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with INVOKANA.

Genital Mycotic Infections: INVOKANA increases the risk of genital mycotic infections. Patients with a history of genital mycotic infections and uncircumcised males were more likely to develop genital mycotic infections *[see Adverse Reactions]*. Monitor and treat appropriately.

Hypersensitivity Reactions: Hypersensitivity reactions (e.g., generalized urticaria), some serious, were reported with INVOKANA treatment; these reactions generally occurred within hours to days after initiating INVOKANA. If hypersensitivity reactions occur, discontinue use of INVOKANA; treat per standard of care and monitor until signs and symptoms resolve *[see Contraindications and Adverse Reactions]*.

Increases in Low-Density Lipoprotein (LDL-C): Dose-related increases in LDL-C occur with INVOKANA *[see Adverse Reactions]*. Monitor LDL-C and treat per standard of care after initiating INVOKANA.

Macrovascular Outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with INVOKANA or any other antidiabetic drug.

ADVERSE REACTIONS

The following important adverse reactions are described below and elsewhere in the labeling:

- Hypotension *[see Warnings and Precautions]*
- Impairment in Renal Function *[see Warnings and Precautions]*
- Hyperkalemia *[see Warnings and Precautions]*
- Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues *[see Warnings and Precautions]*
- Genital Mycotic Infections *[see Warnings and Precautions]*
- Hypersensitivity Reactions *[see Warnings and Precautions]*
- Increases in Low-Density Lipoprotein (LDL-C) *[see Warnings and Precautions]*

Clinical Studies Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to the rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Pool of Placebo-Controlled Trials: The data in Table 1 is derived from four 26-week placebo-controlled trials. In one trial INVOKANA was used as monotherapy and in three trials INVOKANA was used as add-on therapy *[see Clinical Studies (14) in full Prescribing Information]*. These data reflect exposure of 1667 patients to INVOKANA and a mean duration of exposure to

INVOKANA of 24 weeks. Patients received INVOKANA 100 mg (N=833), INVOKANA 300 mg (N=834) or placebo (N=646) once daily. The mean age of the population was 56 years and 2% were older than 75 years of age. Fifty percent (50%) of the population was male and 72% were Caucasian, 12% were Asian, and 5% were Black or African American. At baseline the population had diabetes for an average of 7.3 years, had a mean HbA1C of 8.0% and 20% had established microvascular complications of diabetes. Baseline renal function was normal or mildly impaired (mean eGFR 88 mL/min/1.73 m^2).

Table 1 shows common adverse reactions associated with the use of INVOKANA. These adverse reactions were not present at baseline, occurred more commonly on INVOKANA than on placebo, and occurred in at least 2% of patients treated with either INVOKANA 100 mg or INVOKANA 300 mg.

Table 1: Adverse Reactions From Pool of Four 26–Week Placebo-Controlled Studies Reported in ≥ 2% of INVOKANA-Treated Patients*

Adverse Reaction	Placebo N=646	INVOKANA 100 mg N=833	INVOKANA 300 mg N=834
Female genital mycotic infections†	3.2%	10.4%	11.4%
Urinary tract infections‡	4.0%	5.9%	4.3%
Increased urination§	0.8%	5.3%	4.6%
Male genital mycotic infections¶	0.6%	4.2%	3.7%
Vulvovaginal pruritus	0.0%	1.6%	3.0%
Thirst#	0.2%	2.8%	2.3%
Constipation	0.9%	1.8%	2.3%
Nausea	1.5%	2.2%	2.3%

* The four placebo-controlled trials included one monotherapy trial and three add-on combination trials with metformin, metformin and sulfonylurea, or metformin and pioglitazone.

† Female genital mycotic infections include the following adverse reactions: Vulvovaginal candidiasis, Vulvovaginal mycotic infection, Vulvovaginitis, Vaginal infection, Vulvitis, and Genital infection fungal. Percentages calculated with the number of female subjects in each group as denominator: placebo (N=312), INVOKANA 100 mg (N=425), and INVOKANA 300 mg (N=430).

‡ Urinary tract infections includes the following adverse reactions: Urinary tract infection, Cystitis, Kidney infection, and Urosepsis.

§ Increased urination includes the following adverse reactions: Polyuria, Pollakiuria, Urine output increased, Micturition urgency, and Nocturia.

¶ Male genital mycotic infections include the following adverse reactions: Balanitis or Balanoposthitis, Balanitis candida, and Genital infection fungal. Percentages calculated with the number of male subjects in each group as denominator: placebo (N=334), INVOKANA 100 mg (N=408), and INVOKANA 300 mg (N=404).

Thirst includes the following adverse reactions: Thirst, Dry mouth, and Polydipsia.

Abdominal pain was also more commonly reported in patients taking INVOKANA 100 mg (1.8%), 300 mg (1.7%) than in patients taking placebo (0.8%).

Pool of Placebo- and Active-Controlled Trials: The occurrence of adverse reactions was also evaluated in a larger pool of patients participating in placebo- and active-controlled trials.

The data combined eight clinical trials *[see Clinical Studies (14) in full Prescribing Information]* and reflect exposure of 6177 patients to INVOKANA. The mean duration of exposure to INVOKANA was 38 weeks with 1832 individuals exposed to INVOKANA for greater than 50 weeks. Patients received INVOKANA 100 mg (N=3092), INVOKANA 300 mg (N=3085) or comparator (N=3262) once daily. The mean age of the population was 60 years and 5% were older than 75 years of age. Fifty-eight percent (58%) of the population was male and 73% were Caucasian, 16% were Asian, and 4% were Black or African American. At baseline, the population had diabetes for an average of 11 years, had a mean HbA1C of 8.0% and 33% had established microvascular complications of diabetes. Baseline renal function was normal or mildly impaired (mean eGFR 81 mL/min/1.73 m^2).

The types and frequency of common adverse reactions observed in the pool of eight clinical trials were consistent with those listed in Table 1. In this pool, INVOKANA was also associated with the adverse reactions of fatigue (1.7% with comparator, 2.2% with INVOKANA 100 mg, and 2.0% with INVOKANA 300 mg) and loss of strength or energy (i.e., asthenia) (0.6% with comparator, 0.7% with INVOKANA 100 mg and 1.1% with INVOKANA 300 mg).

In the pool of eight clinical trials, the incidence rate of pancreatitis (acute or chronic) was 0.9, 2.7, and 0.9 per 1000 patient-years of exposure to comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively.

In the pool of eight clinical trials with a longer mean duration of exposure to INVOKANA (68 weeks), the incidence rate of bone fracture was 14.2, 18.7, and 17.6 per 1000 patient years of exposure to comparator, INVOKANA

100 mg, and INVOKANA 300 mg, respectively. Upper extremity fractures occurred more commonly on INVOKANA than comparator.

In the pool of eight clinical trials, hypersensitivity-related adverse reactions (including erythema, rash, pruritus, urticaria, and angioedema) occurred in 3.0%, 3.8%, and 4.2% of patients receiving comparator, INVOKANA 100 mg and INVOKANA 300 mg, respectively. Five patients experienced serious adverse reactions of hypersensitivity with INVOKANA, which included 4 patients with urticaria and 1 patient with a diffuse rash and urticaria occurring within hours of exposure to INVOKANA. Among these patients, 2 patients discontinued INVOKANA. One patient with urticaria had recurrence when INVOKANA was re-initiated.

Photosensitivity-related adverse reactions (including photosensitivity reaction, polymorphic light eruption, and sunburn) occurred in 0.1%, 0.2%, and 0.2% of patients receiving comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively.

Other adverse reactions occurring more frequently on INVOKANA than on comparator were:

Volume Depletion-Related Adverse Reactions: INVOKANA results in an osmotic diuresis, which may lead to reductions in intravascular volume. In clinical studies, treatment with INVOKANA was associated with a dose-dependent increase in the incidence of volume depletion-related adverse reactions (e.g., hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration). An increased incidence was observed in patients on the 300 mg dose. The three factors associated with the largest increase in volume depletion-related adverse reactions were the use of loop diuretics, moderate renal impairment (eGFR 30 to less than 60 mL/min/1.73 m^2) and age 75 years and older (Table 2) *[see Dosage and Administration (2.2) in full Prescribing Information, Warnings and Precautions, and Use in Specific Populations]*.

Table 2: Proportion of Patients With at Least one Volume Depletion-Related Adverse Reactions (Pooled Results from 8 Clinical Trials)

Baseline Characteristic	Comparator Group* %	INVOKANA 100 mg %	INVOKANA 300 mg %
Overall population	1.5%	2.3%	3.4%
75 years of age and older†	2.6%	4.9%	8.7%
eGFR less than 60 mL/min/1.73 m^{2}†	2.5%	4.7%	8.1%
Use of loop diuretic†	4.7%	3.2%	8.8%

***** Includes placebo and active-comparator groups

† Patients could have more than 1of the listed risk factors

Impairment in Renal Function: INVOKANA is associated with a dose-dependent increase in serum creatinine and a concomitant fall in estimated GFR (Table 3). Patients with moderate renal impairment at baseline had larger mean changes.

Table 3: Changes in Serum Creatinine and eGFR Associated with INVOKANA in the Pool of Four Placebo-Controlled Trials and Moderate Renal Impairment Trial

			Placebo N=646	INVOKANA 100 mg N=833	INVOKANA 300 mg N=834
Pool of Four Placebo-Controlled Trials	Baseline	Creatinine (mg/dL)	0.84	0.82	0.82
		eGFR (mL/min/1.73 m^2)	87.0	88.3	88.8
	Week 6 Change	Creatinine (mg/dL)	0.01	0.03	0.05
		eGFR (mL/min/1.73 m^2)	-1.6	-3.8	-5.0
	End of Treatment Change*	Creatinine (mg/dL)	0.01	0.02	0.03
		eGFR (mL/min/1.73 m^2)	-1.6	-2.3	-3.4
			Placebo N=90	**INVOKANA 100 mg N=90**	**INVOKANA 300 mg N=89**
Moderate Renal Impairment Trial	Baseline	Creatinine (mg/dL)	1.61	1.62	1.63
		eGFR (mL/min/1.73 m^2)	40.1	39.7	38.5
	Week 3 Change	Creatinine (mg/dL)	0.03	0.18	0.28
		eGFR (mL/min/1.73 m^2)	-0.7	-4.6	-6.2
	End of Treatment Change*	Creatinine (mg/dL)	0.07	0.16	0.18
		eGFR (mL/min/1.73 m^2)	-1.5	-3.6	-4.0

***** Week 26 in mITT LOCF population

In the pool of four placebo-controlled trials where patients had normal or mildly impaired baseline renal function, the proportion of patients who experienced at least one event of significant renal function decline, defined as an eGFR below 80 mL/min/1.73 m^2 and 30% lower than baseline, was 2.1% with placebo, 2.0% with INVOKANA 100 mg, and 4.1% with INVOKANA 300 mg. At the end of treatment, 0.5% with placebo, 0.7% with INVOKANA 100 mg, and 1.4% with INVOKANA 300 mg had a significant renal function decline.

INVOKANA™ (canagliflozin) tablets

In a trial carried out in patients with moderate renal impairment with a baseline eGFR of 30 to less than 50 mL/min/1.73 m^2 (mean baseline eGFR 39 mL/min/1.73 m^2) *[see Clinical Studies (14.3) in full Prescribing Information]*, the proportion of patients who experienced at least one event of significant renal function decline, defined as an eGFR 30% lower than baseline, was 6.9% with placebo, 18% with INVOKANA 100 mg, and 22.5% with INVOKANA 300 mg. At the end of treatment, 4.6% with placebo, 3.4% with INVOKANA 100 mg, and 3.4% with INVOKANA 300 mg had a significant renal function decline.

In a pooled population of patients with moderate renal impairment (N=1085) with baseline eGFR of 30 to less than 60 mL/min/1.73 m^2 (mean baseline eGFR 48 mL/min/1.73 m^2), the overall incidence of these events was lower than in the dedicated trial but a dose-dependent increase in incident episodes of significant renal function decline compared to placebo was still observed.

Use of INVOKANA was associated with an increased incidence of renal-related adverse reactions (e.g., increased blood creatinine, decreased glomerular filtration rate, renal impairment, and acute renal failure), particularly in patients with moderate renal impairment.

In the pooled analysis of patients with moderate renal impairment, the incidence of renal-related adverse reactions was 3.7% with placebo, 8.9% with INVOKANA 100 mg, and 9.3% with INVOKANA 300 mg. Discontinuations due to renal-related adverse events occurred in 1.0% with placebo, 1.2% with INVOKANA 100 mg, and 1.6% with INVOKANA 300 mg *[see Warnings and Precautions]*.

Genital Mycotic Infections: In the pool of four placebo-controlled clinical trials, female genital mycotic infections (e.g., vulvovaginal mycotic infection, vulvovaginal candidiasis, and vulvovaginitis) occurred in 3.2%, 10.4%, and 11.4% of females treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. Patients with a history of genital mycotic infections were more likely to develop genital mycotic infections on INVOKANA. Female patients who developed genital mycotic infections on INVOKANA were more likely to experience recurrence and require treatment with oral or topical antifungal agents and anti-microbial agents *[see Warnings and Precautions]*.

In the pool of four placebo-controlled clinical trials, male genital mycotic infections (e.g., candidal balanitis, balanoposthitis) occurred in 0.6%, 4.2%, and 3.7% of males treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. Male genital mycotic infections occurred more commonly in uncircumcised males and in males with a prior history of balanitis or balanoposthitis. Male patients who developed genital mycotic infections on INVOKANA were more likely to experience recurrent infections (22% on INVOKANA versus none on placebo), and require treatment with oral or topical antifungal agents and anti-microbial agents than patients on comparators. In the pooled analysis of 8 controlled trials, phimosis was reported in 0.3% of uncircumcised male patients treated with INVOKANA and 0.2% required circumcision to treat the phimosis *[see Warnings and Precautions]*.

Hypoglycemia: In all clinical trials, hypoglycemia was defined as any event regardless of symptoms, where biochemical hypoglycemia was documented (any glucose value below or equal to 70 mg/dL). Severe hypoglycemia was defined as an event consistent with hypoglycemia where the patient required the assistance of another person to recover, lost consciousness, or experienced a seizure (regardless of whether biochemical documentation of a low glucose value was obtained). In individual clinical trials *[see Clinical Studies (14) in full Prescribing Information]*, episodes of hypoglycemia occurred at a higher rate when INVOKANA was co-administered with insulin or sulfonylureas (Table 4) *[see Warnings and Precautions]*.

Table 4: Incidence of Hypoglycemia* in Controlled Clinical Studies

Monotherapy (26 weeks)	**Placebo (N=192)**	**INVOKANA 100 mg (N=195)**	**INVOKANA 300 mg (N=197)**
Overall [N (%)]	5 (2.6)	7 (3.6)	6 (3.0)
In Combination with Metformin (26 weeks)	**Placebo + Metformin (N=183)**	**INVOKANA 100 mg + Metformin (N=368)**	**INVOKANA 300 mg + Metformin (N=367)**
Overall [N (%)]	3 (1.6)	16 (4.3)	17 (4.6)
Severe [N (%)]†	0 (0)	1 (0.3)	1 (0.3)
In Combination with Metformin (52 weeks)	**Glimepiride + Metformin (N=482)**	**INVOKANA 100 mg + Metformin (N=483)**	**INVOKANA 300 mg + Metformin (N=485)**
Overall [N (%)]	165 (34.2)	27 (5.6)	24 (4.9)
Severe [N (%)]†	15 (3.1)	2 (0.4)	3 (0.6)
In Combination with Sulfonylurea (18 weeks)	**Placebo + Sulfonylurea (N=69)**	**INVOKANA 100 mg + Sulfonylurea (N=74)**	**INVOKANA 300 mg + Sulfonylurea (N=72)**
Overall [N (%)]	4 (5.8)	3 (4.1)	9 (12.5)
In Combination with Metformin + Sulfonylurea (26 weeks)	**Placebo + Metformin + Sulfonylurea (N=156)**	**INVOKANA 100 mg + Metformin + Sulfonylurea (N=157)**	**INVOKANA 300 mg + Metformin + Sulfonylurea (N=156)**
Overall [N (%)]	24 (15.4)	43 (27.4)	47 (30.1)
Severe [N (%)]†	1 (0.6)	1 (0.6)	0

Table 4: Incidence of Hypoglycemia* in Controlled Clinical Studies (continued)

In Combination with Metformin + Sulfonylurea (52 weeks)	**Sitagliptin + Metformin + Sulfonylurea (N=378)**		**INVOKANA 300 mg + Metformin + Sulfonylurea (N=377)**
Overall [N (%)]	154 (40.7)		163 (43.2)
Severe [N (%)]†	13 (3.4)		15 (4.0)
In Combination with Metformin + Pioglitazone (26 weeks)	**Placebo + Metformin + Pioglitazone (N=115)**	**INVOKANA 100 mg + Metformin + Pioglitazone (N=113)**	**INVOKANA 300 mg + Metformin + Pioglitazone (N=114)**
Overall [N (%)]	3 (2.6)	3 (2.7)	6 (5.3)
In Combination with Insulin (18 weeks)	**Placebo (N=565)**	**INVOKANA 100 mg (N=566)**	**INVOKANA 300 mg (N=587)**
Overall [N (%)]	208 (36.8)	279 (49.3)	285 (48.6)
Severe [N (%)]†	14 (2.5)	10 (1.8)	16 (2.7)

* Number of patients experiencing at least one event of hypoglycemia based on either biochemically documented episodes or severe hypoglycemic events in the intent-to-treat population

† Severe episodes of hypoglycemia were defined as those where the patient required the assistance of another person to recover, lost consciousness, or experienced a seizure (regardless of whether biochemical documentation of a low glucose value was obtained)

Laboratory Tests: *Increases in Serum Potassium:* Dose-related, transient mean increases in serum potassium were observed early after initiation of INVOKANA (i.e., within 3 weeks) in a trial of patients with moderate renal impairment *[see Clinical Studies (14.3) in full Prescribing Information]*. In this trial, increases in serum potassium of greater than 5.4 mEq/L and 15% above baseline occurred in 16.1%, 12.4%, and 27.0% of patients treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. More severe elevations (i.e., equal or greater than 6.5 mEq/L) occurred in 1.1%, 2.2%, and 2.2% of patients treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. In patients with moderate renal impairment, increases in potassium were more commonly seen in those with elevated potassium at baseline and in those using medications that reduce potassium excretion, such as potassium-sparing diuretics, angiotensin-converting-enzyme inhibitors, and angiotensin-receptor blockers *[see Warnings and Precautions]*.

Increases in Serum Magnesium: Dose-related increases in serum magnesium were observed early after initiation of INVOKANA (within 6 weeks) and remained elevated throughout treatment. In the pool of four placebo-controlled trials, the mean change in serum magnesium levels was 8.1% and 9.3% with INVOKANA 100 mg and INVOKANA 300 mg, respectively, compared to -0.6% with placebo. In a trial of patients with moderate renal impairment *[see Clinical Studies (14.3) in full Prescribing Information]*, serum magnesium levels increased by 0.2%, 9.2%, and 14.8% with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively.

Increases in Serum Phosphate: Dose-related increases in serum phosphate levels were observed with INVOKANA. In the pool of four placebo controlled trials, the mean change in serum phosphate levels were 3.6% and 5.1% with INVOKANA 100 mg and INVOKANA 300 mg, respectively, compared to 1.5% with placebo. In a trial of patients with moderate renal impairment *[see Clinical Studies (14.3) in full Prescribing Information]*, the mean serum phosphate levels increased by 1.2%, 5.0%, and 9.3% with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively.

Increases in Low-Density Lipoprotein Cholesterol (LDL-C) and non-High-Density Lipoprotein Cholesterol (non-HDL-C): In the pool of four placebo-controlled trials, dose-related increases in LDL-C with INVOKANA were observed. Mean changes (percent changes) from baseline in LDL-C relative to placebo were 4.4 mg/dL (4.5%) and 8.2 mg/dL (8.0%) with INVOKANA 100 mg and INVOKANA 300 mg, respectively. The mean baseline LDL-C levels were 104 to 110 mg/dL across treatment groups *[see Warnings and Precautions]*.

Dose-related increases in non-HDL-C with INVOKANA were observed. Mean changes (percent changes) from baseline in non-HDL-C relative to placebo were 2.1 mg/dL (1.5%) and 5.1 mg/dL (3.6%) with INVOKANA 100 mg and 300 mg, respectively. The mean baseline non-HDL-C levels were 140 to 147 mg/dL across treatment groups.

Increases in Hemoglobin: In the pool of four placebo-controlled trials, mean changes (percent changes) from baseline in hemoglobin were -0.18 g/dL (-1.1%) with placebo, 0.47 g/dL (3.5%) with INVOKANA 100 mg, and 0.51 g/dL (3.8%) with INVOKANA 300 mg. The mean baseline hemoglobin value was approximately 14.1 g/dL across treatment groups. At the end of treatment, 0.8%, 4.0%, and 2.7% of patients treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively, had hemoglobin above the upper limit of normal.

DRUG INTERACTIONS

UGT Enzyme Inducers: Rifampin: Co-administration of canagliflozin with rifampin, a nonselective inducer of several UGT enzymes, including UGT1A9, UGT2B4, decreased canagliflozin area under the curve (AUC) by 51%. This decrease in exposure to canagliflozin may decrease efficacy. If an inducer of these UGTs (e.g., rifampin, phenytoin, phenobarbital, ritonavir) must be co-administered with INVOKANA (canagliflozin), consider increasing the dose to 300 mg once daily if patients are currently tolerating INVOKANA 100 mg once daily, have an eGFR greater than 60 mL/min/1.73 m^2, and require additional glycemic control. Consider other antihyperglycemic therapy in patients with an eGFR of 45 to less than 60 mL/min/1.73 m^2 receiving concurrent therapy with a UGT inducer and require additional glycemic control *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3) in full Prescribing Information]*.

Digoxin: There was an increase in the area AUC and mean peak drug concentration (C_{max}) of digoxin (20% and 36%, respectively) when co-administered with INVOKANA 300 mg *[see Clinical Pharmacology (12.3) in full Prescribing Information]*. Patients taking INVOKANA with concomitant digoxin should be monitored appropriately.

USE IN SPECIFIC POPULATIONS

Pregnancy: Teratogenic Effects: Pregnancy Category C: There are no adequate and well-controlled studies of INVOKANA in pregnant women. Based on results from rat studies, canagliflozin may affect renal development and maturation. In a juvenile rat study, increased kidney weights and renal pelvic and tubular dilatation were evident at greater than or equal to 0.5 times clinical exposure from a 300 mg dose *[see Nonclinical Toxicology (13.2) in full Prescribing Information]*.

These outcomes occurred with drug exposure during periods of animal development that correspond to the late second and third trimester of human development. During pregnancy, consider appropriate alternative therapies, especially during the second and third trimesters. INVOKANA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known if INVOKANA is excreted in human milk. INVOKANA is secreted in the milk of lactating rats reaching levels 1.4 times higher than that in maternal plasma. Data in juvenile rats directly exposed to INVOKANA showed risk to the developing kidney (renal pelvic and tubular dilatations) during maturation. Since human kidney maturation occurs *in utero* and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from INVOKANA, a decision should be made whether to discontinue nursing or to discontinue INVOKANA, taking into account the importance of the drug to the mother *[see Nonclinical Toxicology (13.2) in full Prescribing Information]*.

Pediatric Use: Safety and effectiveness of INVOKANA in pediatric patients under 18 years of age have not been established.

Geriatric Use: Two thousand thirty-four (2034) patients 65 years and older, and 345 patients 75 years and older were exposed to INVOKANA in nine clinical studies of INVOKANA *[see Clinical Studies (14.3) in full Prescribing Information]*.

Patients 65 years and older had a higher incidence of adverse reactions related to reduced intravascular volume with INVOKANA (such as hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration), particularly with the 300 mg daily dose, compared to younger patients; more prominent increase in the incidence was seen in patients who were 75 years and older *[see Dosage and Administration (2.1) in full Prescribing Information and Adverse Reactions]*. Smaller reductions in HbA1C with INVOKANA relative to placebo were seen in older (65 years and older; -0.61% with INVOKANA 100 mg and -0.74% with INVOKANA 300 mg relative to placebo) compared to younger patients (-0.72% with INVOKANA 100 mg and -0.87% with INVOKANA 300 mg relative to placebo).

Renal Impairment: The efficacy and safety of INVOKANA were evaluated in a study that included patients with moderate renal impairment (eGFR 30 to less than 50 mL/min/1.73 m^2) *[see Clinical Studies (14.3) in full Prescribing Information]*. These patients had less overall glycemic efficacy and had a higher occurrence of adverse reactions related to reduced intravascular volume, renal-related adverse reactions, and decreases in eGFR compared to patients with mild renal impairment or normal renal function (eGFR greater than or equal to 60 mL/min/1.73 m^2); patients treated with INVOKANA 300 mg were more likely to experience increases in potassium *[see Dosage and Administration (2.2) in full Prescribing Information, Warnings and Precautions, and Adverse Reactions]*.

The efficacy and safety of INVOKANA have not been established in patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m^2), with ESRD, or receiving dialysis. INVOKANA is not expected to be effective in these patient populations *[see Contraindications and Clinical Pharmacology (12.3) in full Prescribing Information]*.

Hepatic Impairment: No dosage adjustment is necessary in patients with mild or moderate hepatic impairment. The use of INVOKANA has not been studied in patients with severe hepatic impairment and is therefore not recommended *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

Voices

Thanks for the tip

I recently read Jim Plagakis' July 2013 column, "Pharmacognosy is an elective worth pursuing." I will be a first-year pharmacy student this fall at Presbyterian College School of Pharmacy. I currently work retail for a chain pharmacy, but I believe I want to do something greater with my pharmacy education.

Reading JP's article has really inspired me. I do not know whether my school offers pharmacognosy as an elective (our first-year classes are scheduled for us) but if they do, I will definitely take the class as a second- or third-year student. I want to thank JP for writing the article and inspiring current pharmacists and future pharmacists, such as myself.

Caleb Staggs
SIMPSONVILLE, S.C.

Don't forget the big picture

I am writing in response to Jim Ober's comments on cigarettes ["Why do drugstores sell products that kill?" Dispensed as Written, May 2013].

I am not for smoking and have never been a smoker, but I am concerned about the fact that slowly our freedoms are being eroded by some people who have very good intentions, but take little thought about the bigger picture.

There are many, many, let's just say unhealthy products that most chain pharmacies carry, cigarettes being one of them.

Just because Pillsbury makes it, and mom served it up does not make it a wonderful product. A few examples: Candy, cookies, ice cream, high-fat milk, soft drinks, potato chips, snack cakes, chocolate in all assorted varieties, and let us not forget alcoholic beverages.

I wonder how many people die from heart disease, diabetes, stroke, or DWI each year because of products that are sold in our drugstores every day? Also, do you think Walmart is going to stop selling cigarettes because Mr. Ober's heart is in the right place? If drugstores discontinue the sale of cigarettes, they will be purchased at other convenience stores or any outlet that Jim says is okay.

We live in America. Our freedoms are precious. Many sacrificed and died so that we could have freedom of choice.

Johnnie F. Hajek Jr., RPh
AUSTIN, TEXAS

Continued on pg. 21

IN MY VIEW Steven R. Ariens, PD

The Hundred Years' War

Our country seems obsessed with "fighting wars": Korean, Vietnam, War on Poverty, No Child Left Behind (a.k.a., War on Illiteracy), and the granddaddy of all wars, THE WAR ON DRUGS. History suggests that the last war we fought that had a final victory was World War II, and that took two H-bombs to bring to a close.

How it began

Unofficially, the war on drugs started with the Harrison Narcotic Act of 1914, which established the Bureau of Narcotics. In 1968, this bureau merged with FDA's Bureau of Drug Abuse Control to become the Bureau of Narcotics and Dangerous Drugs (BNDD). By 1971, the BNDD had 1,500 agents and a budget of $43 million.

In 1973, the BNDD morphed into the Drug Enforcement Administration (DEA), which by 2011 had a total of 10,000 employees and a $2 billion budget.

There is at least one group of former law enforcement officers as well as others in the justice system who believe that the war on drugs is a waste of time: the members of the organization Law Enforcement Against Prohibition *(www.leap.cc).*

PMPs

The first prescription monitoring program (PMP) was funded by one of the pharmaceutical manufacturers; however, most of the laws that created these programs in the various states prohibited data mining to uncover doctor- and pharmacy-shoppers.

Today, these databases operate in real time and transmission of data is transparent, from the pharmacy point of view.

Unfortunately, retrieval of reports on patients is, to say the very least, time-consuming. It makes one wonder why the data goes in easily, but getting reports out of the system is just the opposite.

It has been reported that several of the chain pharmacies do not allow their prescription departments to have access to the internet, which is the only way to retrieve a report from the PMP. Is that because they don't want staff wasting time running reports — or because they don't want to lose any revenue, which would happen if pharmacists rejected prescriptions from doctor- and pharmacy-shoppers?

The big glitch

Then there is a major flaw in the entire PMP system: Healthcare professionals must accept the patient's ID at face value — but anyone can obtain fake ID nowadays.

The general public's access to technology has surpassed the original intent of the PMP program. Just Google "how to create fake driver's license" to see how easy it is to get the material and instructions.

On October 4, 2010, the *Boston Globe* reported the case of a man who stole dozens of IDs and used them to fill forged prescriptions all over Massachusetts (http://b.globe.com/172k3Qn).

The case involved 76 counts of stolen IDs, 76 counts of forged prescriptions, and 40 counts of insurance fraud. And that's just one example.

There's more

I learned a few years ago in an e-mail from the Indiana Board of Pharmacy that the Indiana PMP asked the state's Bureau of Motor Vehicles to allow a cross-reference of the IDs in the PMP database against the state's BMV database, in order to validate the IDs in the PMP database. This was denied by the BMV, and the decision was supported by the state's attorney general. How many other state PMPs have encountered similar obstacles?

Spiked guns in the war on drugs

So the war on drugs is being fought with:

- A system that uses a PMP that has unknown number of forged IDs
- Many employers who will not provide internet access to pharmacists so that they can use the PMP
- PMPs that mandate transparent submission of data but don't mandate easy retrieval of reports
- A system that will not provide for an easy way to validate the IDs of new patients seeking controlled meds against an official database
- An untold number of healthcare professionals who do not want to be the "police."

Then there is the DEA, whose charge, we assume, is to prevent the diversion of drugs. A DEA agent has told me that in fact, its purpose is to arrest those who divert, and I believe it.

Follow the money

If you follow the money trail, everyone from pharmaceutical manufacturers to physicians to pharmacies — *everyone* — stands to profit from the flow of money connected with the prescribing and selling of controlled drugs. And the DEA can justify larger budgets and job security by pointing to the continued flow of drugs getting to the street. DT

Steve Ariens *is National Public Relations Director for The Pharmacy Alliance (www.the pharmacyalliance.com). E-mail him at steve@stevearіens.com or check out his blog,* Pharmacist Steve *(http://www.pharmaciststeve.com/).*

Voices

Continued from pg. 17

Where are the watchdogs?

In a recent Voices column ["You get what you pay for," June 2013], Robert Katz questioned the safety of pharmaceutical products manufactured abroad.

I agree with Mr Katz 100%. It seems that no one else is too concerned that nearly all the generic drugs and most of the brand-name drugs are made in other countries, so that pharmaceutical companies and CEOs can reap the benefits (profits).

I have my doubts that FDA even checks all the companies overseas. I guess that is evident with Ranbaxy!

I have been in the pharmacy profession since 1966 and have seen a lot of changes, some good and some bad, the bad being the movement of drug manufacture to other countries. I can remember when pharmaceuticals salesmen would come by and check your stock, write up returns, and take orders, or just tell you about a new drug that was coming out.

The drug reps were like family. I remember Abbott Labs, Wyeth, Lederle, MSD, Upjohn, A.H. Robins, Schering, SKF, and a few more. I have not seen a company rep in years.

We should have known what was happening when the Big Store started advertising $4/month prescriptions.

Eddie Davis, RPh
WAXAHACHIE, TEXAS

Corrections: *The last line of the first column on page 18 of the August 2013 print issue (Up Front) was inadvertently omitted. Referring to Julie A. Johnson, PharmD, the complete quote reads, "She is the ideal person to help leverage the extensive strengths of the College of Pharmacy to enhance the mission of UF Health and the university." On page 47 of the same issue, in the item "Dabigatran has new boxed warning," the manufacturer and URL for dabigatran were misidentified; they are Boehringer Ingelheim and pradaxapro.com. Lastly, the acronym HIPAA was misspelled on the August cover.* Drug Topics *regrets the errors.*

We want to hear from you

Printed and e-mailed letters should be brief and include the writer's name, address, daytime phone number, and date of the issue you are referencing: Editor, ***Drug Topics***, 24950 Country Club Blvd., Suite 200, North Olmsted, OH 44070-5351. E-mail address: drugtopics@advanstar.com. Letters may be edited for length, style, content, and clarity at our discretion.

VIEW FROM THE ZOO David Stanley, RPh

Pharmacist on the spot

I used to have a friend who claimed *The New York Times* was the best pharmacy journal out there, and he subscribed just for that reason. All the big drug companies are major Fortune 500 corporations trading on the New York Stock Exchange, and with the ins and outs of healthcare always on everyone's minds, his plan was to learn most of what he needed to know about the profession by keeping tabs on the business and health news printed in the nation's paper of record.

I thought of him the other day as I browsed the paper's website and came across an article that resonated right at the heart of modern pharmacy practice.

Here's the gist: In reaction to the passage of restrictive new abortion laws in the state of Texas, more women are expected to cross the border into Mexico, where Mexican pharmacists sell an "abortion pill" over the counter.

That pill is misoprostol, known to most of those reading this as the anti-ulcer medication Cytotec. That it can be used to end a pregnancy has been an open secret in the medical community for years, but it was the following quote that really caught my eye:

"When asked how women should use the pills, some of the pharmacists said they did not know and others recommended wildly different regimes that doctors say could be unsafe."

These are words to strike horror into the heart of any pharmacy academic or leader north of the border. Evidently the Mexican Pharmaceutical Association is even less effective at addressing the needs of the profession than is its counterpart in the United States.

Key roles

I bring this up not to start a debate in these pages on the abortion issue, but to point out how one story in a mainstream paper neatly tied together most of the issues facing pharmacy today.

It illustrated simultaneously the reality that pharmacists are the most accessible of healthcare professionals and the importance of our roles as educators and guides to proper medication use.

If the article also had talked about the imposition of flu-shot quotas and the pressure to meet assembly-line metrics in the filling of patients' prescriptions, it would have covered in one fell swoop every challenge we face.

Here's the beef

I also bring up this subject so that you can be ready.

The passage of laws making access to abortion harder to obtain in parts of this country is not going to let up any time soon.

This means that between striving to meet that shot quota and the "prescriptions-filled-within-15-minutes-of label-print" metric, one day soon you may very well find yourself faced with a question from a scared and vulnerable young woman about a pill she got from the local flea market to "bring her period back."

No matter where you stand on one of this country's most divisive issues, I doubt that you would want to see any young woman put herself in harm's way through incorrect use of that medication.

This means that we'll have to come up with a better answer than "I don't know."

And it will have to be a better answer than "Call your doctor," since for some of these patients, talking to a doctor might be as big a challenge as flying to the moon.

Ready or not

Welcome to the world of "beyond count, pour, lick, and stick." Whether you're ready or not, it's coming to your counter, in ways you may not have expected or been trained for.

For all the talk of fancy prescription MTM and cookbook immunization protocols, sometimes our value arises from the fact that the pharmacist is the only patient contact who might prevent a medication-induced disaster.

You can't measure it or put a quota on it, but it's the most important thing we do.

Make sure you're ready. DT

David Stanley *is a pharmacy owner, blogger, and professional writer in northern California. Contact him at drugmonkeyrph@gmail.com.*

RID®

HAS EVERYTHING YOU NEED TO STOP LICE

The RID Complete Lice Elimination Kit contains:

- **RID Lice Killing Shampoo** is 100% effective in eliminating lice*

Kit also contains:

- **Patented RIDvantage® Lice Comb** is 100% effective at removing lice eggs†
- **RID Lice & Egg Comb-Out Gel** helps facilitate lice and egg removal
- **RID Home Lice, Bedbug & Dust Mite Spray** kills lice and eggs on bedding and furniture

Shampoo, Spray, and Comb may be purchased separately

Recommend RID — everything you need to stop lice — with confidence

Use as directed.

*Based on clinical studies (Data on file). Reapplication of RID shampoo and egg removal are required for complete effectiveness. See label for important information

†Combing result demonstrated in a laboratory study performed by trained testers.

For Professional and Consumer Support

1-800-RID-LICE www.ridlicepro.com

Pharmacists on front lines for improved U.S. healthcare system, Clinton says

During the NACDS Total Store Expo, held in Las Vegas on August 12, keynote speaker Hillary Rodham Clinton praised pharmacists for being on the front lines to help improve the U.S. healthcare system as well as to implement the Affordable Care Act (ACA).


Hillary Clinton

Clinton, former secretary of state, former U.S. senator from New York, and former first lady, acknowledged that the ACA was not a perfect law and that its implementation would not be perfect either. However, she stressed, the act was "a landmark achievement for the Obama administration" and pharmacists will be instrumental in making it work by educating millions of uninsured Americans about enrollment.

Twenty years ago this month, via a satellite link to the NACDS meeting, Clinton had thanked pharmacists for being advocates for a common-sense approach to finding solutions to meet a host of healthcare challenges, including quality, affordability, and cost.

"I personally believe that if we work together and follow the example of many of you who are trying to figure out how to serve the people who come into your pharmacy and store every day, we will make progress together," she said.

She recalled the difficulty with the implementation of Medicare Part D, the prescription drug benefit, and how instrumental pharmacists were to ensuring access for Medicare beneficiaries.

Now with the enrollment of millions of Americans under the ACA, starting in October, pharmacists will have greater opportunities to provide direct healthcare services to patients.

"We need to ask ourselves how we can replace our fee-for-service model with provider-led, community-wide care that can compete on quality and reward value over volume. These are difficult questions and we have been wrestling with them for over 20 years. If we work together and discuss and negotiate in good faith, we will find the answers," Clinton said.

It will take leadership, not in Washington, DC, but in the private sector that is collaborative, innovative, and inclusive. Leaders need to decide that compromise is not a dirty word, she said.

"Each of you has a chance to help us find the answers and exercise leadership," she said.

Keynote speaker Hillary Rodham Clinton urged pharmacists to support ACA at the NACDS Total Store Expo.

LEGALIZATION

Illinois adopts medical marijuana law

Illinois has become the 21st state to legalize some form of medical marijuana with the establishment of a four-year pilot program that targets patients with chronic pain and debilitating conditions such as muscular dystrophy, cancer, and HIV.

The Compassionate Use of Medical Cannabis Pilot Program Act is described as one of the most-restrictive medical marijuana laws in the country. It was signed into law by Governor Pat Quinn on August 1 and will take effect in 2014.

"This new law will provide relief and help eligible patients ease their suffering, while making sure Illinois has the nation's strictest safeguards to prevent abuse," Quinn said.

Under the pilot program, doctors with patients suffering from one of 35 chronic conditions will be authorized to issue certifications for the drug. Patients will be required to apply for a registry identification card that will track how much marijuana they buy; the upper limit is 2.5 ounces within 14 days.

Marijuana will be grown at 22 cultivation centers throughout Illinois and up to 60 centers will dispense it. Patients will not be allowed to grow their own.

Patients who wish to be part of the program must meet other regulations as well. For example, the physician and patient must have an established relationship. Minors and people with felony drug convictions or psychiatric conditions will not qualify. Police and probation officers, firefighters, and school bus drivers are ineligible. Marijuana may not be used on a school bus or on school grounds, in a correctional facility, in a residence used to provide childcare, or any public place. And landlords retain the right to ban the smoking of medical cannabis on leased property.

"Patients afflicted by the most unbearable conditions finally have a compassionate answer to their cries for help," said Sen. Bill Haine (D-Alton). "This program alleviates suffering and provides strong safeguards against abuse. We are ensuring only those suffering from the most serious diseases receive this treatment."

Indication

Osphena™ (ospemifene) is indicated for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.

Select Important Safety Information

Boxed WARNING: Endometrial Cancer and Cardiovascular Disorders

Osphena is an estrogen agonist/antagonist with tissue selective effects. In the endometrium Osphena has estrogen agonistic effects. There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogen therapy. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding.

The Women's Health Initiative (WHI) estrogen-alone substudy reported an increased risk of stroke and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) during 7.1 years of treatment with daily oral conjugated estrogens (CE) [0.625 mg], relative to placebo. Osphena 60 mg had thromboembolic and hemorrhagic stroke incidence rates of 0.72 and 1.45 per thousand women vs. 1.04 and 0 per thousand women for placebo and a DVT incidence rate of 1.45 vs. 1.04 per thousand women for placebo. Osphena should be prescribed for the shortest duration consistent with treatment goals and risks for the individual woman.

Please see additional Important Safety Information and Brief Summary of the Full Prescribing Information, including Boxed WARNING, on the following pages.

Select Important Safety Information

Contraindications

- Osphena should not be used in patients with undiagnosed abnormal genital bleeding, known or suspected estrogen-dependent neoplasia, active deep vein thrombosis (DVT), pulmonary embolism (PE) or active arterial thromboembolic disease or a history of these conditions
- Women who are or may become pregnant. Osphena may cause fetal harm when administered to a pregnant woman. Ospemifene was embryo-fetal lethal with labor difficulties and increased pup deaths in rats at doses below clinical exposures, and embryo-fetal lethal in rabbits at 10 times the clinical exposure based on mg/m^2. If this drug is used during pregnancy, or if a woman becomes pregnant while taking this drug, she should be apprised of the potential hazard to a fetus

Warnings and Precautions

Osphena has not been adequately studied in women with breast cancer; therefore it should not be used in women with known or suspected breast cancer or with a history of breast cancer.

Osphena should not be used in women with severe hepatic impairment as it has not been studied.

In clinical trials the more commonly reported adverse reactions in ≥1 percent of patients treated with Osphena 60 mg compared to placebo were: hot flush (7.5% vs. 2.6%), vaginal discharge (3.8% vs. 0.3%), muscle spasms (3.2% vs. 0.9%), hyperhidrosis (1.6% vs. 0.6%), and genital discharge (1.3% vs. 0.1%).

Do not use estrogens or estrogen agonists/antagonists, fluconazole, or rifampin concomitantly with Osphena.

Please see Brief Summary of the Full Prescribing Information, including Boxed WARNING, on the following page.

The first and only NON-ESTROGEN ORAL treatment for moderate to severe dyspareunia, due to menopause

- **REVERSES** key physiological signs of vulvar and vaginal atrophy (VVA), which include increasing superficial cells, decreasing parabasal cells, and decreasing vaginal pH
- Significantly **IMPROVED** the most bothersome symptom (MBS)* of VVA, which was moderate to severe dyspareunia
- Available in a 60-mg **ORAL** tablet taken once daily with food
- Most common adverse reactions include hot flush, vaginal discharge, muscle spasms, hyperhidrosis, and genital discharge

NLY The **FIRST** FDA-approved estrogen agonist/antagonist for moderate to severe dyspareunia, due to menopause.

New Osphena™
(ospemifene) tablets
60 mg

STUDY DESIGN: Two 12-week, randomized, double-blind, placebo-controlled, parallel-group efficacy studies in 1745 generally healthy postmenopausal women. The first clinical study included 3 treatment groups: Osphena 30 mg (n=282), Osphena 60 mg (n=276), and placebo (n=268). The second clinical study included 2 treatment groups: Osphena 60 mg (n=463) and placebo (n=456). Clinical endpoints for both clinical studies included: a mean change from baseline to Week 12 for percentage of superficial cells on a vaginal smear, percentage of parabasal cells on a vaginal smear, vaginal pH, and most bothersome symptom of VVA (dyspareunia) self-reported by the patient.* A 52-week, randomized, double-blind, placebo-controlled, long-term safety study was also conducted with 2 treatment groups: Osphena 60 mg (n=363) and placebo (n=63).

*MBS was defined as the most bothersome moderate to severe symptom at baseline.

osphena.com

OSPHENA™ (ospemifene) 60 mg tablets
BRIEF SUMMARY – See Package Insert for Complete Prescribing Information.

WARNING: ENDOMETRIAL CANCER AND CARDIOVASCULAR DISORDERS

Endometrial Cancer

OSPHENA is an estrogen agonist/antagonist with tissue selective effects. In the endometrium, OSPHENA has estrogen agonistic effects. There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. Adding a progestin to estrogen therapy reduces the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Adequate diagnostic measures, including directed and random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding [see *Warnings and Precautions (5.2)*].

Cardiovascular Disorders

There is a reported increased risk of stroke and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) who received daily oral conjugated estrogens (CE) [0.625 mg]-alone therapy over 7.1 years as part of the Women's Health Initiative (WHI) [see *Warnings and Precautions (5.1)*].

In the clinical trials for OSPHENA (duration of treatment up to 15 months), the incidence rates of thromboembolic and hemorrhagic stroke were 0.72 and 1.45 per thousand women, respectively in OSPHENA 60 mg treatment group and 1.04 and 0 in placebo [see *Warnings and Precautions (5.1)*]. The incidence of DVT was 1.45 per thousand women in OSPHENA 60 mg treatment group and 1.04 per thousand women in placebo [see *Warnings and Precautions (5.1)*]. OSPHENA should be prescribed for the shortest duration consistent with treatment goals and risks for the individual woman.

INDICATIONS AND USAGE: OSPHENA is indicated for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.

CONTRAINDICATIONS: OSPHENA is contraindicated in women with any of the following conditions:
- Undiagnosed abnormal genital bleeding
- Known or suspected estrogen-dependent neoplasia
- Active DVT, pulmonary embolism (PE), or a history of these conditions
- Active arterial thromboembolic disease [for example, stroke and myocardial infarction (MI)], or a history of these conditions
- OSPHENA is contraindicated in women who are or may become pregnant. OSPHENA may cause fetal harm when administered to a pregnant woman. Ospemifene was embryo-fetal lethal with labor difficulties and increased pup deaths in rats at doses below clinical exposures, and embryo-fetal lethal in rabbits at 10 times the clinical exposure based on mg/m^2. If this drug is used during pregnancy, or if a woman becomes pregnant while taking this drug, she should be apprised of the potential hazard to a fetus.

WARNINGS AND PRECAUTIONS

Cardiovascular Disorders

Risk factors for cardiovascular disorders, arterial vascular disease (for example, hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or venous thromboembolism (VTE) (for example, personal history or family history of VTE, obesity, and systemic lupus erythematosus), should be managed appropriately.

Stroke

In the WHI estrogen-alone substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily CE (0.625 mg)-alone compared to women in the same age group receiving placebo (45 versus 33 per ten thousand women-years). The increase in risk was demonstrated in year 1 and persisted.

In the clinical trials for OSPHENA (duration of treatment up to 15 months), the incidence rates of thromboembolic and hemorrhagic stroke were 0.72 and 1.45 per thousand women, respectively in OSPHENA 60 mg treatment group and 1.04 and 0 per thousand women in placebo.

Should thromboembolic or hemorrhagic stroke occur or be suspected, OSPHENA should be discontinued immediately.

Coronary Heart Disease

In the WHI estrogen-alone substudy, no overall effect on coronary heart disease (CHD) events (defined as non-fatal MI, silent MI, or CHD death) was reported in women receiving estrogen-alone compared to placebo. In the OSPHENA clinical trials, a single MI occurred in a woman receiving 60 mg of ospemifene.

Venous Thromboembolism

In the WHI estrogen-alone substudy, the risk of VTE (DVT and PE), was increased for women receiving daily CE (0.625 mg)-alone compared to placebo (30 versus 22 per ten thousand women-years), although only the increased risk of DVT reached statistical significance (23 versus 15 per ten thousand women-years). The increase in VTE risk was demonstrated during the first 2 years.

In the OSPHENA clinical trials, the incidence of DVT was 1.45 per thousand women in OSPHENA 60 mg treatment group and 1.04 per thousand women in placebo. Should a VTE occur or be suspected, OSPHENA should be discontinued immediately.

If feasible, OSPHENA should be discontinued at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

Malignant Neoplasms

Endometrial Cancer

OSPHENA is an estrogen agonist/antagonist with tissue selective effects. In the endometrium, OSPHENA has agonistic effects. In the OSPHENA clinical trials (60 mg treatment group), no cases of endometrial cancer were seen with exposure up to 52 weeks. There was a single case of simple hyperplasia without atypia. Endometrial thickening equal to 5 mm or greater was seen in the OSPHENA treatment groups at a rate of 60.1 per thousand women vs 21.2 per thousand women for placebo. The incidence of any type of proliferative (weakly plus active plus disordered) endometrium was 86.1 per thousand women in OSPHENA vs 13.3 per thousand women for placebo. Uterine polyps occurred at an incidence of 5.9 per thousand women vs 1.8 per thousand women for placebo.

An increased risk of endometrial cancer has been reported with the use of unopposed estrogen therapy in a woman with a uterus. The reported endometrial cancer risk among unopposed estrogen users is about 2 to 12 times greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with the use of estrogens for less than 1 year. The greatest risk appears to be associated with prolonged use, with increased risks of 15- to 24-fold for 5 to 10 years or more. This risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued. Adding a progestin to postmenopausal estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. There are, however, possible risks that may be associated with the use of progestins with estrogens compared to estrogen-alone regimens. These include an increased risk of breast cancer. The use of progestins with OSPHENA therapy was not evaluated in the clinical trials.

Clinical surveillance of all women using OSPHENA is important. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding.

Breast Cancer

OSPHENA 60 mg has not been adequately studied in women with breast cancer; therefore it should not be used in women with known or suspected breast cancer or with a history of breast cancer.

Severe Hepatic Impairment

OSPHENA should not be used in women with severe hepatic impairment [see Use in Specific Populations (8.7), and Clinical Pharmacology (12.3)].

ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:
- Cardiovascular Disorders [see *Boxed Warnings, Warnings and Precautions (5.1)*]
- Malignant Neoplasms [see *Boxed Warnings, Warnings and Precautions (5.2)*]

Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of OSPHENA has been assessed in nine phase 2/3 trials (N=1892) with doses ranging from 5 to 90 mg per day. The duration of treatment in these studies ranged from 6 weeks to 15 months. Most women (N=1370) had a treatment period of at least 12 weeks, 409 had at least 52 weeks (1 year) of exposure.

The incidence rates of thromboembolic and hemorrhagic stroke were 0.72 per thousand women (1 reported case of thromboembolic stroke) and 1.45 per thousand women (2 reported cases of hemorrhagic stroke), respectively in OSPHENA 60 mg treatment group and 1.04 and 0 per thousand women, respectively in placebo. The incidence of deep vein thrombosis (DVT) was 1.45 per thousand women in OSPHENA 60 mg treatment group (2 reported cases of DVT) and 1.04 (1 case of DVT) in placebo.

In clinical trials the more commonly reported adverse reactions in ≥1 percent of patients treated with Osphena 60 mg compared to placebo were: hot flush (7.5% vs. 2.6%), vaginal discharge (3.8% vs. 0.3%), muscle spasms (3.2% vs. 0.9%), hyperhidrosis (1.6% vs. 0.6%), and genital discharge (1.3% vs. 0.1%).

DRUG INTERACTIONS

OSPHENA is primarily metabolized by CYP3A4 and CYP2C9. CYP2C19 and other pathways contribute to the metabolism of ospemifene.

Estrogens and estrogen agonist/antagonist

OSPHENA should not be used concomitantly with estrogens and estrogen agonists/antagonists. The safety of concomitant use of OSPHENA with estrogens and estrogen agonists/antagonists has not been studied.

Fluconazole

Fluconazole, a moderate CYP3A/strong CYP2C9/moderate CYP2C19 inhibitor, should not be used with OSPHENA. Fluconazole increases the systemic exposure of ospemifene by 2.7-fold. Administration of fluconazole with ospemifene may increase the risk of OSPHENA-related adverse reactions [see *Clinical Pharmacology (12.3)*].

Rifampin

Rifampin, a strong CYP3A4/moderate CYP2C9/moderate CYP2C19 inducer, decreases the systemic exposure of ospemifene by 58%. Therefore, coadministration of OSPHENA with drugs such as rifampin which induce CYP3A4, CYP2C9 and/or CYP2C19 activity would be expected to decrease the systemic exposure of ospemifene, which may decrease the clinical effect [see *Clinical Pharmacology (12.3)*].

Ketoconazole

Ketoconazole, a strong CYP3A4 inhibitor increases the systemic exposure of ospemifene by 1.4-fold. Administration of ketoconazole chronically with ospemifene may increase the risk of OSPHENA-related adverse reactions [see *Clinical Pharmacology (12.3)*].

Warfarin

Repeated administration of ospemifene had no effect on the pharmacokinetics of a single 10 mg dose of warfarin. No study was conducted with multiple doses of warfarin. The effect of ospemifene on clotting time such as the International Normalized Ratio (INR) or prothrombin time (PT) was not studied [see *Clinical Pharmacology (12.3)*].

Highly Protein-Bound Drugs

Ospemifene is more than 99% bound to serum proteins and might affect the protein binding of other drugs. Use of OSPHENA with other drug products that are highly protein bound may lead to increased exposure of either that drug or ospemifene [see *Clinical Pharmacology (12.3)*].

Multiple Enzyme Inhibition

Coadministration of OSPHENA with a drug known to inhibit CYP3A4 and CYP2C9 isoenzymes may increase the risk of OSPHENA-related adverse reactions.

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic effects: Pregnancy Category X [see *Contraindications (4)*].

Nursing Mothers

It is not known whether OSPHENA is excreted in human breast milk. In a nonclinical study, ospemifene was excreted in rat milk and detected at concentrations higher than that in maternal plasma.

Pediatric Use

OSPHENA is not indicated in children. Clinical studies have not been conducted in the pediatric population.

Geriatric Use

Of the 1892 OSPHENA-treated women enrolled in the nine phase 2/3 trials of OSPHENA, >19 percent were 65 years of age or older. No clinically meaningful differences in safety or effectiveness were observed between these women and younger women less than 65 years of age.

Renal Impairment

The pharmacokinetics of ospemifene in women with severe renal impairment (CrCL<30 mL/min) was similar to those in women with normal renal function [see *Clinical Pharmacology (12.3)*].

No dose adjustment of OSPHENA is required in women with renal impairment.

Hepatic Impairment

The pharmacokinetics of ospemifene has not been studied in women with severe hepatic impairment (Child-Pugh Class C); therefore, OSPHENA should not be used in women with severe hepatic impairment [see *Warnings and Precautions (5.3)*, and *Clinical Pharmacology (12.3)*].

No clinically important pharmacokinetic differences with OSPHENA were observed between women with mild to moderate hepatic impairment and healthy women [see *Clinical Pharmacology (12.3)*].

No dose adjustment of OSPHENA is required in women with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment.

OVERDOSAGE

There is no specific antidote for OSPHENA.

Based on OSPHENA (ospemifene) 60 mg tablets, Prescribing Information 02/2013.

SHIONOGI INC.

SHIONOGI INC.

HYPERTENSION AND SODIUM

Blood pressure response to dietary sodium is reproducible over long term

Blood pressure (BP) response to changes in dietary sodium and potassium is reproducible over the long term and may help identify candidates at risk for hypertension and cardiovascular disease, according to a study published in the journal *Hypertension*.

Researchers tested BP responses of 487 Chinese study participants for four to five years. Previous clinical studies had examined the reproducibility of BP responses only to dietary sodium change over the short term, with inconsistent results. "To the best of our knowledge, this is the first study to investigate the long-term reproducibility of salt sensitivity and potassium sensitivity of BP," wrote Dongfeng Gu, from the Department of Population Genetics and Prevention, Fu Wai Hospital and Cardiovascular Institute, Beijing, China, and colleagues.

The study

During the Genetic Epidemiology Network of Salt Sensitivity (GenSalt) study, approximately 1,800 individuals between the ages of 18 and 60 years in rural northern China completed the initial three-week dietary sodium and potassium interventions during October 2003 and July 2005. In the follow-up, 487 participants were retested about four and a half years later.

The dietary interventions were the same for the initial part of the study and the follow-up. After the three-day baseline observation period, participants adhered to a low-salt diet for seven days (3 g of salt or 51.3 mmol of sodium daily) and then a high-salt diet for another seven days (18 g of salt or 307.8 mmol of sodium per day). In the final week, daily potassium supplementation (60-mmol potassium) was added to the high-salt diet.

During the observation period and the interventions on days 5, 6, and 7 in the initial study and follow-up study, BP measurements were taken nine times at each intervention for a mean BP level. Compliance was validated with urinalysis.

Results

The results showed BP levels declined from baseline with the low-salt diet, increased with high salt, and declined with high salt/daily potassium supplements in the first and follow-up studies.

"BP responses to changes in dietary sodium and potassium are not random phenomena but stable and reproducible human characteristics over a relatively long time period," the researchers wrote. "These findings have potentially important clinical and public health implications. High dietary sodium intake is a major risk factor for hypertension. Population-based sodium reduction should be complemented by targeted sodium reduction among individuals who are more sensitive to sodium."

The authors suggested that future studies should focus on the identification of simple biomarkers for classifying sodium and potassium sensitivity in humans. Identification of individuals with these sensitivities may help in risk prediction and treatment of hypertension and cardiovascular diseases.

TURF WAR

Rx crackdown pitting pharmacists against doctors

As the Drug Enforcement Agency (DEA) increases scrutiny of pharmacies dispensing controlled substances that are sometimes illegally diverted, new policies designed to curb prescription abuse are pitting pharmacists against physicians.

As evidenced by the $80 million fine recently levied against Walgreens for record-keeping and dispensing violations, DEA has set it sights squarely on pharmacies and pharmacists that have, willingly or not, contributed to the huge problem of Rx abuse and fraud. In some cases, the feds have also targeted doctors who write bogus prescriptions.

In response, Walgreens and others have taken steps to stem the fraud and abuse, including requiring pharmacists to verify some scripts for controlled substances by contacting prescribers. This has delayed some dispensing, upsetting some customers and physicians.

The American Medical Association (AMA) recently weighed in on the issue by passing a strongly worded resolution criticizing telephone calls from pharmacists requesting additional information about pain medication Rxs.

The resolution stated that AMA "deem[s] inappropriate inquiries from pharmacies to verify the medical rationale behind prescriptions, diagnoses, and treatment plans to be an interference with the practice of medicine and unwarranted."

It further threatens that AMA might "advocate for legislative and regulatory solutions to prohibit pharmacies and pharmacists from denying medically necessary and legitimate therapeutic treatments to patients."

Pharmacy groups respond

Several pharmacy groups responded to the AMA rebuke. The National Community Pharmacists Association's response called the resolution "short-sighted" and "simplistic."

"We support a collective approach to controlling abuse and diversion that involves everyone: Patient, pharmacist, pharmacy benefit manager, wholesaler, manufacturer, and prescriber," NCPA stated. NCPA further noted that the Department of Health and Human Services' Office of the Inspector General recently identified more than 700 physicians who exhibited questionable prescribing patterns and called for better education for prescribers.

Kasey Thompson, PharmD, vice president of policy, planning and communications, American Society of Health-System Pharmacists, said AMA and pharmacy groups must collaborate to stem the problem. "The bottom line is that there is a major prescription drug abuse epidemic in this country and we need to find more ways to work together as a healthcare community to solve it," Thompson said in a published report.

COMBINATION THERAPY

Naltrexone plus prolonged exposure therapy helps alcohol-dependent PTSD patients

In a study of patients with alcohol dependence and posttraumatic stress disorder (PTSD), treatment with naltrexone resulted in a decrease in the percentage of patient-drinking days. Prolonged exposure therapy was not associated with an exacerbation of alcohol-use disorder.

Lead author Edna B. Foa, professor of psychology in psychiatry and director, Center for the Treatment and Study of Anxiety, University of Pennsylvania Perelman School of Medicine, examined the effects of naltrexone, a medication used in alcohol-use re-education, and prolonged exposure, the most validated psychosocial treatment for PTSD, and their combination in individuals with comorbid alcohol dependence and PTSD. Patients were randomly assigned to one of four treatments: prolonged exposure, naltrexone, prolonged exposure plus naltrexone, and pill placebo. All patients received supportive counseling.

Findings

"Naltrexone was effective in decreasing the percentage of days drinking in people with alcohol dependence and posttraumatic stress disorder during active treatment," said Foa. "Six months after treatment discontinuation, participants who received prolonged exposure therapy for PTSD drank less than those who did not receive prolonged exposure. Participants who received a combined treatment of prolonged exposure and naltrexone had the lowest drinking level after six-month treatment discontinuation. The main message of the study is that simultaneous treatment of alcohol dependence and PTSD yields a superior outcome than each treatment would alone."

The study was conducted to examine the validity of the common view in the field that treating patients with alcohol dependence in ways that deal directly with their traumatic experience will result in deterioration of their mental health and cause them to drink more rather than less, Foa said.

"The findings of the study indicated that prolonged exposure therapy, a trauma-focused treatment for PTSD, was not associated with increased drinking or alcohol craving," she said. "In fact, reduction in PTSD severity and drinking was evident for all four treatment groups. This finding contradicts the common view that trauma-focused therapy is contraindicated for individuals with alcohol dependence and PTSD, because it may exacerbate PTSD symptoms and thereby lead to increased alcohol use.

"Patients with comorbid PTSD and alcohol dependence should receive treatment that addresses simultaneously the two disorders rather than treatment that addresses only one of the two disorders," she continued. "Prolonged exposure therapy for PTSD helps patients maintain a low level of drinking rather than increasing drinking and therefore should be provided to these patients."

PATH TO BETTER HEALTH

CVS launches online drug information resource for consumers

In August, CVS/pharmacy introduced a new online Drug Information Center at its website, *www.cvs.com*, offering consumers a variety of innovative resources to better manage their health. The new center provides detailed information about prescription and nonprescription medications, and vitamins and supplements, as well as a drug interaction tool to help discover how a prescription drug or over-the-counter product interacts with other medications and lifestyle factors.

"As a pharmacy innovation company, we are constantly exploring new tools and resources to help our customers on their path to better health. With this launch, we are offering users medication expertise in a simple, interactive way that provides relevant and personalized drug information that has never been made available to them before," said Brian Tilzer, senior vice president, chief digital officer for CVS/pharmacy, in a prepared statement.

The Drug Information Center offers drug information enhanced with new medication overviews that include images of the drug products and videos showing how the drug works when consumed. "This helps patients understand how the medication works so they will keep taking it even if they do not feel an immediate physical difference," a CVS/pharmacy press statement said.

In addition, the center offers rates of side effects and patient usage statistics, including their severity and when to become concerned about potential side effects. Patients can also review typical dosage strengths and the average generic vs. brand-name drug usage rates.

Drug interaction tool

Another feature enables consumers to access a personalized drug interaction checker to find out whether/how prescription medication or OTC products interact with other medications and lifestyle factors. Users can easily import their prescription information from their *www.cvs.com* accounts or manually enter the information. Users can make a comprehensive review of possible interactions and refine their searches with filters for severity of interactions or by specific medications. This new feature is similar to the innovative Drug Interaction Checker that was recently added to the CVS/pharmacy mobile app for smartphones.

Printable medicine list

Consumers can also note their prescription and nonprescription health information on a printable medicine list that can be easily folded into a wallet-sized card and made readily available for sharing with pharmacists, physicians, and other healthcare providers at the point of service.

CVS/pharmacy plans to add more enhancements to its website and the Drug Information Center, including a variety of new elements for its digital offerings.

For Active, Mild to Moderate Ulcerative Colitis (UC)

UCERIS™: POWER PATIENTS CAN HANDLE

- UCERIS is a locally acting form of budesonide[1]
- **MMX® technology** targets delivery of budesonide throughout the full length of the colon[1,2]
- **3 times** more patients taking UCERIS achieved combined clinical remission **and** mucosal healing compared with placebo[3]*
- Rates of overall expected glucocorticoid-related side effects were similar for UCERIS and placebo at 8 weeks—10.2% vs 10.5%, respectively[1]*
- UCERIS is conveniently dosed as a single 9-mg tablet, taken once daily for up to 8 weeks[1]

Contact your wholesaler to order today!

- **Supplied in bottles of 30 tablets[1]**
- **NDC 68012-309-30[1]**
- **No AB-rated equivalent for UCERIS[4]**

Tablet is not actual size.

INDICATIONS AND USAGE

UCERIS™ is a glucocorticosteroid indicated for the induction of remission in patients with active, mild to moderate ulcerative colitis.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

UCERIS is contraindicated in patients with known hypersensitivity to budesonide or any of the ingredients of UCERIS.

WARNINGS AND PRECAUTIONS

- Hypercorticism and adrenal suppression: Since UCERIS is a glucocorticosteroid, general warnings concerning glucocorticoids should be followed.
- Transferring patients from systemic corticosteroids: Risk of impaired adrenal function when transferring from oral steroids with high systemic effects. Taper patients slowly from systemic corticosteroids if transferring to UCERIS.
- Immunosuppression: Potential worsening of infections (eg, existing tuberculosis, fungal, bacterial, viral, or parasitic infection; or ocular herpes simplex). Use with caution in patients with these infections. More serious or even fatal course of chickenpox or measles can occur in susceptible patients.
- Increased systemic glucocorticoid susceptibility: Reduced liver function affects the elimination of glucocorticosteroids.
- Other glucocorticoid effects: Caution should be taken in patients with hypertension, diabetes mellitus, osteoporosis, peptic ulcer, glaucoma or cataracts, or with a family history of diabetes or glaucoma, or with any other condition where glucocorticosteroids may have unwanted effects.

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥2%) are headache, nausea, decreased blood cortisol, upper abdominal pain, fatigue, flatulence, abdominal distension, acne, urinary tract infection, arthralgia, and constipation.

DRUG INTERACTIONS

Avoid Cytochrome P450 3A4 inhibitors (eg, ketoconazole, grapefruit juice). May cause increased systemic corticosteroid effects.

USE IN SPECIFIC POPULATIONS

Hepatic impairment: Monitor patients for signs and/or symptoms of hypercorticism.

The Important Safety Information does not include all the information needed to use UCERIS safely and effectively. Please see Brief Summary of Prescribing Information on the following pages and Full Prescribing Information at www.UCERIS.com.

CORE study design: Two randomized, double-blind, placebo-controlled studies were conducted in a total of 899 adult patients with active, mild to moderate UC (Ulcerative Colitis Disease Activity Index [UCDAI]: ≥4 and ≤10 at entry). The primary endpoint was induction of combined clinical remission and mucosal healing (defined as a UCDAI score of ≤1, with scores of 0 for both rectal bleeding and stool frequency, normal mucosa with no friability on endoscopy, and a ≥1-point reduction in the Endoscopic Index score) after 8 weeks of treatment.[1]

*In a pooled analysis of 2 Phase III clinical trials.[1,3]

References: 1. UCERIS Prescribing Information. Santarus, Inc. January 2013. **2.** Brunner M, Ziegler S, Di Stefano AF, et al. Gastrointestinal transit, release and plasma pharmacokinetics of a new oral budesonide formulation. *Br J Clin Pharmacol.* 2005;61:31-38. **3.** Data on file. Santarus, Inc. **4.** US Food and Drug Administration. Drugs at FDA Web site. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. Accessed April 24, 2013.

SANTARUS, INC.®

www.UCERIS.com/Pharmacy

UCERIS™
(budesonide) extended release tablets

BRIEF SUMMARY
Please see package insert for Full Prescribing Information available at www.uceris.com
UCERIS (budesonide) extended release tablets, for oral use
Rx Only

INDICATIONS AND USAGE UCERIS (budesonide) extended release tablets are indicated for the induction of remission in patients with active, mild to moderate ulcerative colitis.

CONTRAINDICATIONS UCERIS is contraindicated in patients with hypersensitivity to budesonide or any of the ingredients of UCERIS. Anaphylactic reactions have occurred with other budesonide formulations.

WARNINGS AND PRECAUTIONS

Hypercorticism and Adrenal Axis Suppression When glucocorticosteroids are used chronically, systemic effects such as hypercorticism and adrenal suppression may occur. Glucocorticosteroids can reduce the response of the hypothalamus-pituitary-adrenal (HPA) axis to stress. In situations where patients are subject to surgery or other stress situations, supplementation with a systemic glucocorticosteroid is recommended. Since UCERIS is a glucocorticosteroid, general warnings concerning glucocorticoids should be followed. **Transferring Patients from Systemic Glucocorticosteroid Therapy** Care is needed in patients who are transferred from glucocorticosteroid treatment with higher systemic effects to glucocorticosteroids with lower systemic effects, such as UCERIS, since symptoms attributed to withdrawal of steroid therapy, including those of acute adrenal suppression or benign intracranial hypertension, may develop. Adrenocortical function monitoring may be required in these patients and the dose of glucocorticosteroid treatment with high systemic effects should be reduced cautiously. **Immunosuppression** Patients who are on drugs that suppress the immune system are more susceptible to infection than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in susceptible patients or patients on immunosuppressant doses of glucocorticosteroids. In patients who have not had these diseases, particular care should be taken to avoid exposure. How the dose, route and duration of glucocorticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior glucocorticosteroid treatment to the risk is also not known. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See prescribing information for VZIG and IG.) If chicken pox develops, treatment with antiviral agents may be considered. Glucocorticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infection, untreated fungal, bacterial, systemic viral or parasitic infections. Replacement of systemic glucocorticosteroids with UCERIS tablets may unmask allergies (e.g., rhinitis and eczema), which were previously controlled by the systemic drug. **Increased Systemic Glucocorticoid Susceptibility** Reduced liver function affects the elimination of glucocorticosteroids, and increased systemic availability of oral budesonide has been demonstrated in patients with liver cirrhosis. **Other Glucocorticosteroid Effects** Caution should be taken in patients with hypertension, diabetes mellitus, osteoporosis, peptic ulcer, glaucoma or cataracts, or with a family history of diabetes or glaucoma, or with any other condition where glucocorticosteroids may have unwanted effects.

ADVERSE REACTIONS

Systemic glucocorticosteroid use may result in the following:

- Hypercorticism and Adrenal Suppression
- Symptoms of steroid withdrawal in those patients transferring from Systemic Glucocorticosteroid Therapy
- Immunosuppression
- Increased Systemic Glucocorticosteroid Susceptibility
- Other Glucocorticosteroid Effects

Clinical Trials Experience Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The safety of UCERIS has been evaluated in controlled and open-label clinical trials which enrolled a combined total of 1105 patients with ulcerative colitis. In two 8-week, placebo-controlled studies in patients with active disease (Study 1 and Study 2), a total of 255 patients received UCERIS 9 mg, 254 patients received UCERIS 6 mg, and 258 patients received placebo. They ranged in age from 18-77 years (mean 43), 56% were male, and 75% were Caucasian. The most common adverse reactions were headache, nausea, decreased blood cortisol, upper abdominal pain, fatigue, flatulence, abdominal distension, acne, urinary tract infection, arthralgia, and constipation. The adverse reactions occurring in 2% or more of patients on therapy with UCERIS 9 mg are summarized in Table 1.

Table 1. Summary of Adverse Reactions in Two Placebo Controlled Trials Experienced by at Least 2% of the UCERIS 9 mg Group (Studies 1 and 2)

	UCERIS 9 mg (N = 255) n (%)	UCERIS 6 mg (N = 254) n (%)	Placebo (N = 258) n (%)
Headache	29 (11.4)	37 (14.6)	27 (10.5)
Nausea	13 (5.1)	12 (4.7)	11 (4.3)
Decreased Blood Cortisol	11 (4.3)	6 (2.4)	1 (0.4)
Upper Abdominal Pain	10 (3.9)	8 (3.1)	5 (1.9)
Fatigue	8 (3.1)	5 (2.0)	5 (1.9)
Flatulence	6 (2.4)	8 (3.1)	5 (1.9)
Abdominal Distension	6 (2.4)	4 (1.6)	2 (0.8)
Acne	6 (2.4)	2 (0.8)	5 (1.9)
Urinary Tract Infection	5 (2.0)	1 (0.4)	1 (0.4)
Arthralgia	5 (2.0)	5 (2.0)	4 (1.6)
Constipation	5 (2.0)	1 (0.4)	2 (0.8)

Of UCERIS 9 mg patients, a total of 15% discontinued treatment due to any adverse event (including adverse reactions) compared with 17% in the placebo group. Table 2 summarizes the percentages of patients reporting glucocorticoid related effects in the 2 placebo-controlled studies.

Table 2. Summary of Glucocorticoid Related Effects in Two Placebo-Controlled Trials (Studies 1 and 2)

	UCERIS 9 mg (N = 255) n (%)	UCERIS 6 mg (N = 254) n (%)	Placebo (N = 258) n (%)
Overall	26 (10.2)	19 (7.5)	27 (10.5)
Mood changes	9 (3.5)	10 (3.9)	11 (4.3)
Sleep changes	7 (2.7)	10 (3.9)	12 (4.7)
Insomnia	6 (2.4)	6 (2.4)	8 (3.1)
Acne	6 (2.4)	2 (0.8)	5 (1.9)
Moon face	3 (1.2)	3 (1.2)	4 (1.6)
Fluid retention	2 (0.8)	3 (1.2)	3 (1.2)
Hirsutism	1 (0.4)	0	0
Striae rubrae	0	0	2 (0.8)
Flushing	0	1 (0.4)	3 (1.2)

No clinically significant differences were observed with respect to the overall percentages of patients with any glucocorticoid related effects between UCERIS and placebo after 8 weeks of induction therapy. Study 3 was an open-label study evaluating UCERIS 9 mg once daily for 8 weeks in 60 patients who had previously completed an 8-week induction study (Study 1), but had not achieved remission. Among patients who took UCERIS 9 mg up to 16 weeks cumulatively across Study 1 and Study 3 combined, similar rates of adverse reactions and glucocorticoid-related effects were seen compared to those who took UCERIS 9 mg for 8 weeks in Study 1. In Study 4, the safety of long-term treatment with UCERIS 6 mg was evaluated in a placebo-controlled 12-month maintenance study of 123 patients. Patients who had previously completed 8 weeks of therapy in any induction study (Study 1, 2, or 3) and were in remission were randomized to UCERIS 6 mg or placebo once daily for 12 months. In patients who took UCERIS 6 mg for up to 12 months, similar rates of adverse reactions were seen between placebo and UCERIS 6 mg. After up to 12 months of study treatment, 77% (27/35) of the patients in the UCERIS 6 mg and 74% (29/39) of the patients in the placebo treatment groups had normal bone density scans. In Study 4, the glucocorticoid related effects were similar in patients with up to 12 months of therapy with UCERIS 6 mg and placebo. (Table 3)

Table 3. Summary of Glucocorticoid Related Effects Over 12-month Treatment (Study 4)

	UCERIS 6 mg (N = 62) n (%)	Placebo (N = 61) n (%)
Overall	9 (14.5)	7 (11.5)
Insomnia	4 (6.5)	4 (6.6)
Mood changes	4 (6.5)	2 (3.3)
Moon face	3 (4.8)	3 (4.9)
Sleep changes	3 (4.8)	3 (4.9)
Acne	3 (4.8)	0
Hirsutism	3 (4.8)	0
Flushing	1 (1.6)	1 (1.6)
Fluid retention	1 (1.6)	1 (1.6)

Postmarketing Experience The following adverse reactions have been identified during postapproval use of oral budesonide. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. *Immune System Disorders:* anaphylactic reactions *Nervous System Disorders:* benign intracranial hypertension *Psychiatric Disorders:* mood swings

DRUG INTERACTIONS

Interaction with CYP3A4 inhibitors Concomitant oral administration of ketoconazole (a known inhibitor of CYP3A4 activity in the liver and in the intestinal mucosa) caused an eight-fold increase of the systemic exposure to oral budesonide. If treatment with inhibitors of CYP3A4 activity (such as ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, erythromycin) is indicated, discontinuation of UCERIS should be considered. After extensive intake of grapefruit juice (which inhibits CYP3A4 activity predominantly in the intestinal mucosa), the systemic exposure for oral budesonide increased about two times. Ingestion of grapefruit or grapefruit juice should be avoided in connection with UCERIS administration. **Inhibitors of Gastric Acid Secretion** Since the dissolution of the coating of UCERIS is pH dependent, the release properties and uptake of the compound may be altered when UCERIS is used after treatment with gastric acid reducing agents (e.g., PPIs, H2 blockers and antacids).

USE IN SPECIFIC POPULATIONS

Pregnancy *Teratogenic Effects: Pregnancy Category C* Budesonide was teratogenic and embryocidal in rabbits and rats. Budesonide produced fetal loss, decreased pup weights, and skeletal abnormalities at subcutaneous doses of 25 mcg/kg in rabbits (approximately 0.05 times the maximum recommended human dose on a body surface area basis) and 500 mcg/kg in rats (approximately 0.5 times the maximum recommended human dose on a body surface area basis). There are no adequate and well-controlled studies in pregnant women. Budesonide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. *Nonteratogenic Effects:* Hypoadrenalism may occur in infants born of mothers receiving glucocorticosteroids during pregnancy. Such infants should be carefully observed. **Nursing Mothers** The disposition of budesonide when delivered by inhalation from a dry powder inhaler at doses of 200 or 400 mcg twice daily for at least 3 months was studied in eight lactating women with asthma from 1 to 6 months postpartum. Systemic exposure to budesonide in these women appears to be comparable to that in non-lactating women with asthma from other studies. Breast milk obtained over eight hours post-dose revealed that the maximum budesonide concentration for the 400 and 800 mcg total daily doses was 0.39 and 0.78 nmol/L, respectively, and occurred within 45 minutes after inhalation. The estimated oral daily dose of budesonide from breast milk to the infant is approximately 0.007 and 0.014 mcg/kg/day for the two dose regimens used in this study, which represents approximately 0.3% to 1% of the dose inhaled by the mother. Budesonide plasma concentrations obtained from five infants at about 90 minutes after breast feeding (and about 140 minutes after drug administration to the mother) were below quantifiable levels (<0.02 nmol/L in four infants and <0.04 nmol/L in one infant). The recommended daily dose of UCERIS extended release tablets is higher (9 mg daily) compared with inhaled budesonide (up to 800 µg daily) given to mothers in the above study. The maximum budesonide plasma concentration following a 9 mg daily dose (in both single- and repeated-dose pharmacokinetic studies) of oral budesonide is approximately 5-10 nmol/L which is up to 10 times higher than the 1-2 nmol/L for an 800 mcg daily dose of inhaled budesonide at steady state in the above inhalation study. Since there are no data from controlled trials on the use of UCERIS by nursing mothers or their infants, and because of the potential for serious adverse reactions in nursing infants from UCERIS, a decision should be made whether to discontinue nursing or to discontinue UCERIS, taking into account the clinical importance of UCERIS to the mother. Budesonide, is secreted in human milk. Data from budesonide delivered via dry powder inhaler indicates that the total daily oral dose of budesonide available in breast milk to the infant is approximately 0.3% to 1% of the dose inhaled by the mother. Assuming the coefficient of extrapolation between the inhaled and oral doses is constant across all dose levels, at therapeutic doses of UCERIS, budesonide exposure to the nursing child may be up to 10 times higher than that by budesonide inhalation. **Pediatric Use** Safety and effectiveness of UCERIS in pediatric patients have not been established. Glucocorticosteroids, such as UCERIS may cause a reduction of growth velocity in pediatric patients. **Geriatric Use** Clinical studies of UCERIS did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, UCERIS should be used cautiously in elderly patients due to the potential for decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. **Hepatic Impairment** Patients with moderate to severe liver disease should be monitored for increased signs and/or symptoms of hypercorticism. Discontinuing the use of UCERIS tablets should be considered in these patients.

OVERDOSAGE

Reports of acute toxicity and/or death following overdosage of glucocorticosteroids are rare. Treatment consists of immediate gastric lavage or emesis followed by supportive and symptomatic therapy. If glucocorticosteroids are used at excessive doses for prolonged periods, systemic glucocorticosteroid effects such as hypercorticism and adrenal suppression may occur. For chronic overdosage in the face of severe disease requiring continuous steroid therapy, the dosage may be reduced temporarily. Single oral budesonide doses of 200 and 400 mg/kg were lethal in female and male mice, respectively. The signs of acute toxicity were decreased motor activity, piloerection and generalized edema.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility *Carcinogenicity* Carcinogenicity studies with budesonide were conducted in rats and mice. In a two-year study in Sprague-Dawley rats, budesonide caused a statistically significant increase in the incidence of gliomas in male rats at an oral dose of 50 mcg/kg (approximately 0.05 times the maximum recommended human dose on a body surface area basis). In addition, there were increased incidences of primary hepatocellular tumors in male rats at 25 mcg/kg (approximately 0.023 times the maximum recommended human dose on a body surface area basis) and above. No tumorigenicity was seen in female rats at oral doses up to 50 mcg/kg (approximately 0.05 times the maximum recommended human dose on a body surface area basis). In an additional two-year study in male Sprague-Dawley rats, budesonide caused no gliomas at an oral dose of 50 mcg/kg (approximately 0.05 times the maximum recommended human dose on a body surface area basis). However, it caused a statistically significant increase in the incidence of hepatocellular tumors at an oral dose of 50 mcg/kg (approximately 0.05 times the maximum recommended human dose on a body surface area basis). The concurrent reference glucocorticosteroids (prednisolone and triamcinolone acetonide) showed similar findings. In a 91-week study in mice, budesonide caused no treatment-related carcinogenicity at oral doses up to 200 mcg/kg (approximately 0.1 times the maximum recommended human dose on a body surface area basis). *Mutagenesis* Budesonide was not genotoxic in the Ames test, the mouse lymphoma cell forward gene mutation ($TK^{+/-}$) test, the human lymphocyte chromosome aberration test, the *Drosophila melanogaster* sex-linked recessive lethality test, the rat hepatocyte UDS test and the mouse micronucleus test. *Impairment of Fertility* In rats, budesonide had no effect on fertility at subcutaneous doses up to 80 mcg/kg (approximately 0.07 times the maximum recommended human dose on a body surface area basis). However, it caused a decrease in prenatal viability and viability in pups at birth and during lactation, along with a decrease in maternal body-weight gain, at subcutaneous doses of 20 mcg/kg (approximately 0.02 times the maximum recommended human dose on a body surface area basis) and above. No such effects were noted at 5 mcg/kg (approximately 0.005 times the maximum recommended human dose on a body surface area basis).

SANTARUS, INC.®

UCERIS™ is a trademark of Santarus, Inc.

U.S. Patent Nos: 7,410,651; 7,431,943; RE43799; 8,293,273.

1-UCE13033 V1

Up front
In Depth

Erin Albert, PharmD, JD, MBA

21 ways to boost medication adherence

The $290 billion problem of medication adherence is one of the top challenges to pharmacy practice.

According to Jim O'Donnell, pharmacist and chief pharmacy executive at Community Health Network in Indianapolis, Ind., "Medication access and adherence are huge but mostly unknown national concerns. When 40% or more of patients with a chronic disease fail to take their medications as prescribed, the consequences are staggering. A reduction in the patient's quality of life, unnecessary emergency room visits, and hospitalizations add more on to our national healthcare costs. We must figure out a way to improve."

A partnership

Seeking a way to get pharmacists in the Indianapolis area thinking deeply about medication adherence, O'Donnell approached Butler University College of Pharmacy and Health Sciences (COPHS). He met with Dr. Julie Koehler, associate dean for clinical education and external affiliations, and her team to discuss the idea of a live CE program.

"At Butler University, we loved the idea of working with Jim and Community Health Network to co-sponsor a live CE program for pharmacists across several practice settings in the Indianapolis area, to share ideas on improving medication adherence," said Koehler.

"However," she continued, "we not only wanted to host a continuing professional development program for pharmacists that was educational; we also wanted it to be a little quirky and fun, in order for it to be memorable — to make it 'edutaining.'"

21 flavors

The result of the collaboration was a half-day CE program for pharmacists titled "21 flavors: Ideas on how we might increase medication adherence." The first CE program was held at Butler University on July 25, 2013.

Each of 21 speakers had five minutes to present an idea on how to encourage medication adherence. Speakers were gonged when their time was up, a strategic maneuver designed to keep the room energized and the exchange of ideas going.

To make each of the 21 ideas more memorable, each speaker had to choose a "flavor" for his or her talk. After each set of three talks, program participants were given five minutes to reflect upon the ideas presented and ask themselves whether each idea could be used in their own practice settings.

After all 20 speakers (one speaker presented two ideas) offered their suggestions for improvement of medication adherence, participants were asked try one of the 21 ideas in their own practice settings within three months of the live program. Follow-up assessments will gather information on the ideas each participant tried and on their results.

Outcomes

Presenters and participants enjoyed the novel presentation.

Butler faculty member Dr. Alison Walton commented, "Fun! Great idea! We should do more of this and expand … sharing and collaboration!"

Dave Burand, a CVS pharmacist and Butler preceptor, said, "It was fun, creative, and as thought-provoking a day as I have spent in a long while."

O'Donnell concluded, "We'd love to see all pharmacists and other providers put on their thinking caps and address the challenge of medication adherence. It would be great to start developing momentum in addressing access and adherence concerns. By sharing the 21 ideas that came out of this meeting, we hope to spread the 'idea virus' on medication adherence to all healthcare professionals, including pharmacists."

Q&A

Here are the suggestions made by the 20 presenters.

1. *How might we help engage children diagnosed with asthma and their parent in the asthma-management process?*

Read a children's book on asthma.
– Dr. Erin Albert

2. *How might we engage children in an asthma action plan?*

Create an interactive game on tablets for children, integrating a game with an asthma action plan.
– Dr. Sarah Saft

3. *How might we engage patients in conversation with motivational interviewing (MI)?*

Use Care management Central (for training staff on MI) and Health Coach 4 Me (for patients).
– Dr. Laura Buelt

Continued on pg. 30

21 ways to boost medication adherence

Continued from pg. 29

4. *How might we predict irrational behavior of patients in medication adherence?*

Understand irrational behavior by reading the book Predictably Irrational.

– Dr. Nick Sciacca

5. *How might we teach pharmacy students empathy for patients regarding medication adherence?*

Require a pillbox simulation assignment for students.

– Dr. Alison Walton

6. *How might we quickly assess patients' health literacy before counseling?*

Use the Rapid Estimate of Adult Literacy in Medicine – Short Form and USP's Pictogram library.

– Dr. Kate Klyczek

7. *How might we help patients perform a complete medication reconciliation and keep an accurate medication list?*

Write an Excel Spreadsheet, or use MedCoach app or My Med List for smartphones.

– Dr. Tracy Costello

8. *How might we put choice forward in healthcare to engage and empower patients?*

Offer dosage-form options to patients for their medications.

– Joe Holman

9. *How might we unearth what truly motivates our patients to be healthy and take their medications?*

Find true motivations for each patient, as they are different.

– Dr. Julie Koehler

10. *How might we improve communication between the pharmacist and the physician?*

Pick up the phone and call when a patient doesn't pick up his meds.

– Dr. Stewart Brown

11. *How might we help patients swallow their medications?*

Instruct them to take several drinks prior to taking medications; to eat soft foods such as Jell-o or applesauce; and then to take the medications — and not to crush medications without asking a pharmacist first.

– Dr. Eric Farmer

12. *How might we eliminate silos in healthcare?*

Collaborate through partnerships like The Community Health Network and Walgreens Take Care Clinics, with shared EMRs.

– Dr. Stacey Bailey

13. *How might we make medications more affordable for patients?*

A medication assistance program (MAP); and creating an accurate medication list, especially when patients shop at many pharmacies.

– Jennifer Koehler

14. *How might we as pharmacists help our patients put their medications into pillboxes?*

Use pharmacy pillboxes with color-coordinated lids on vials with boxes. In the future, use wireless pillbox-filling data delivered wirelessly.

– Dr. Megan Dorrell

15. *How might we use technology such as texting to improve medication adherence?*

Help patients set reminders on their phones, or use technology like FrontlineSMS.

– Dr. Lisa Fletcher

16. *How might we get to know different patients with different disease-state challenges with medication adherence?*

Use the 4/5As of smoking cessation with all patients.

– Dr. Kathleen Haynes

17. *How might we have automatic medlists with practical, usable information for patients?*

MyChart in EPIC is a start from the handwritten med list; *MedActionPlan.com* is also a tool.

– Dr. Emily Papineau

18. H*ow might we help patients manage their medications via smartphone app for free?*

Try My Med Schedule mobile app (for patients, this is a free application).

– Dr. Joe Owen

19. *How might we make medication packaging more patient-friendly and faster to use?*

Switch from multiple-dose containers to single-dose containers from drug manufacturers.

– Jim O'Donnell

20. H*ow might we use wearable technology to improve our patients' healthcare?*

Recommend Jawbone UP wristbands, Pebble: E-Paper watch, Google Glass, and other wearables to patients.

– Jim O'Donnell

21. *How might we decrease hospital readmissions resulting from poor medication adherence?*

Ensure that patients leave the hospital with the medications they need.

– Dr. Alex Ansar

Erin Albert *is assistant professor and director of continuing education at Butler University College of Pharmacy and Health Sciences. To watch the CE proceedings online, go to* https://sites.google.com/a/butler.edu/21-flavors-butler/.

Up front » In Depth

Tracey Walker, Contributing Editor

Ample vaccine supply key to combating unpredictability of flu season

The only predictable aspect of the influenza season is its unpredictability, according to experts.

For example, the 2012-2013 influenza season was a moderately severe influenza season that started early and lasted longer than a usual influenza season. On the other hand, the 2011-2012 year was a mild flu season.

"The best way to be prepared for the upcoming influenza season is to ensure that there is an ample vaccine supply, it is available early and throughout the season, that influenza vaccine be strongly recommended by healthcare providers for all individuals six months of age and older, and there is adequate coverage and reimbursement by insurance providers," said Pedro Piedra, MD, professor, department of molecular virology & microbiology at Baylor College of Medicine, Houston.

"Prevention through vaccination is key to being prepared for the unpredictable nature of the influenza season," Piedra said.

What's new

The 2013-2014 influenza season is the first time that quadrivalent influenza vaccines will be available in the United States. Previously, only trivalent influenza vaccines were available, which contained two influenza A strains and one influenza B strain. Since 2001, influenza B strains from two different lineages (B/Yamagata and B/Victoria) have co-circulated each influenza season in the United States.

Trivalent vaccine formulations rely on predictions of which influenza B strains will be dominant in the upcoming season. However, B strain circulation has been difficult to predict correctly, and in six of the last 12 flu seasons, the vaccine B strain did not match the dominant circulating B strain.

FluMist

MedImmune, the global biologics arm of AstraZeneca, began shipping FluMist Quadrivalent, its intranasal live influenza vaccine, the last week of July to distributors across the United States for the 2013-2014 flu season. FluMist Quadrivalent is the first and only quadrivalent flu vaccine in a nasal spray formulation approved by FDA to help protect against four influenza strains contained in the vaccine: two influenza A strains and two influenza B lineages.

FluMist Quadrivalent replaces MedImmune's FluMist intranasal trivalent influenza vaccine. A needle-free option for eligible individuals (2-49 years of age), FluMist Quadrivalent is administered as a mist sprayed into the nose, the site at which the influenza virus usually enters the body. The most common side effects of FluMist Quadrivalent are runny or stuffy nose, sore throat, and fever over 100° F.

First doses of FluMist Quadrivalent shipped the week of July 22. The product is available through private healthcare practices; public health departments; select retail pharmacies, including Target and Walgreens; hospitals; school-located vaccination programs; military bases; and other sites.

Fluarix/FluLaval

GlaxoSmithKline has begun shipping its Fluarix and FluLaval Quadrivalent intramuscular vaccines, both now approved for use in all individuals three years of age and older. While GSK anticipates making a limited amount of FluLaval Quadrivalent available this influenza season (up to 10 million doses), trivalent versions of both vaccines are also available and shipping. GSK expects to provide between 22 million and 24 million doses of all its vaccines for this flu season. In 2014, GSK's expanded manufacturing capacity will provide "substantial quantities" of quadrivalent influenza vaccine shots to the U.S. market.

Fluvirin/Flucelvax

In mid-August, Novartis began shipment to the United States of an expected minimum of 30 million doses of its flu virus vaccines, including Fluvirin, approved for use in people four years of age and older, and Flucelvax, approved for use in adults 18 years of age and older. Novartis plans to complete most of its shipments of Fluvirin and Flucelvax by October, in advance of the peak of influenza season. Flucelvax, the first influenza vaccine manufactured using cell-based technology to be approved by the FDA, offers a new option to consumers who may prefer it to manufacture using chicken eggs. Flucelvax contain no antibiotics and no preservatives.

Fluzone

Sanofi Pasteur began shipping its Fluzone vaccine late in July. Sanofi Pasteur offers four Fluzone options, including the Fluzone vaccine, the Fluzone quadrivalent vaccine, the Fluzone high-dose vaccine, and the Fluzone intradermal vaccine. The company plans to deliver a total of 60 million doses this fall.

Other FDA-approved influenza virus vaccines for the 2013-2014 season include Afluria, from Merck/CSL, and Flublok, the first influenza vaccine produced with the help of an insect virus and recombinant DNA technology, from Protein Sciences Corporation. DT

Mike Carmody

Pharmacy immunizations: How to manage a successful claims process

From aspirin to milk to makeup, people can get just about anything at their local drug store. Now healthcare joins the list, as more pharmacies offer expanded medical services, including screenings and immunizations.

In light of this past winter's influenza epidemic, which proved to be the nation's worst in the past 10 years, immunizations give retailers a significant opportunity to provide enhanced services to their patients.

And the flu shot is just one type of immunization. Pharmacies now offer other vaccinations that previously were available only at doctors' offices, such as those for hepatitis A, HPV, and TDAP. In fact, Emdeon, as a major processor of vaccination/immunization eligibility and claims transactions, saw a more than 500% increase in these transactions between the 2011 and 2012 seasons.

Early communications

Some challenges do accompany these enhanced service opportunities. Pharmacies face a significant learning curve when contracting with health plans for these services: Immunizations are not regarded as a pharmacy benefit, with which pharmacy retailers are more accustomed, but are regarded as a medical benefit. Without strong payer relationships, pharmacy retailers risk disrupting customer service and losing out on revenue if they can't adequately process vaccination claims.

With the flu season right around the corner, pharmacies should engage payers as early in the year as possible to ensure adequate time to finalize contracting, fully test their billing capabilities, and stock inventory before the official start of the vaccine season. Since the timing is often late summer or early fall, this also provides pharmacies with time to communicate their offerings to patients through targeted marketing efforts well in advance.

Preparation

Pharmacies that begin billing for immunizations often encounter workflow challenges because employees who deal with the public don't understand medical benefit rules or how to accurately process these transactions, including eligibility requests. Patients who are eligible to receive immunizations, therefore, may be erroneously charged for the service or turned away outright, which can injure the pharmacy-patient relationship.

To avoid such problems, pharmacies can thoroughly train their staffs on how to decipher medical cards, submit eligibility requests, and accurately process claims. They should also implement a workflow that may allow easy access in the store to health plans' online portals.

Pharmacies shouldn't hesitate to reach out to health plans and clearinghouses for assistance along the way. Certain clearinghouses provide comprehensive guides that educate pharmacies on how to fulfill a medical claim, to ensure that they collect pertinent information, including legal name, tax identification number, group and individual National Provider Identifiers (NPIs), and transaction destination data such as service location and billing address. Failure to include the right data could result in a suspended or denied claim.

Retail pharmacies should test all transaction types, creating mock eligibility requests or claim submissions, which will allow them to work the kinks out of their processes well before the first patient asks for a vaccination.

Growth opportunity

Immunizations can represent a tremendous growth area for pharmacies: It's estimated that less than half of all Americans receive a flu shot in any given year. Meanwhile, just 19.7% of adults who received a vaccination did so in a pharmacy in 2012, according to CDC records. And history suggests that the number of vaccinations tends to spike in the year following a flu epidemic (such as the one that occurred this past winter).

Pharmacies should remember, however, that product and service expansions can lead to unexpected challenges for both the pharmacy and the payer. With help from clearinghouses, pharmacies are able to solidify their payer relationships and enhance the member experience by ensuring that the entire immunization process, from vaccine delivery to health plan billing, is a seamless one.

And immunizations are just the tip of the iceberg. Strong health-plan relationships give pharmacies a foot in the door to contract for other clinical services. In the quest for more coordinated, consumer-friendly care, payers and pharmacies could collaborate on activities such as disease management and wellness counseling for health plan members.

These offerings provide cost-savings opportunities for payers and help increase foot traffic for the retailer, inviting greater revenue from front-of-store sales and creating the potential for other clinical services in the future. DT

Mike Carmody *is director of DME/MedRx pharmacy services at Emdeon, where he is responsible for pharmacy solution product development and workflow efficiencies.*

While all albuterol may be the same

ONE QUICK-RELIEF INHALER IS DIFFERENT

ProAir® HFA (albuterol sulfate) offers a complete package of helpful features including a built-in dose counter[1]

- Patients know how many puffs are left[1] and when to refill
- A longer-duration, less forceful, warmer plume[2] may give patients more time to inhale
- Storage flexibility and portability[1,3,4] means no need to reprime if dropped

ProAir HFA (albuterol sulfate) Inhalation Aerosol is indicated in patients 4 years of age and older for the treatment or prevention of bronchospasm with reversible obstructive airway disease and for the prevention of exercise-induced bronchospasm.

Important Safety Information

- Inhaled albuterol sulfate can produce paradoxical bronchospasm that may be life-threatening. It should be recognized that paradoxical bronchospasm, when associated with inhaled formulations, frequently occurs with the first use of a new canister
- Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs in patients with asthma
- ProAir HFA, as with all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders (especially coronary insufficiency, cardiac arrhythmias, and hypertension), convulsive disorders, hyperthyroidism, and diabetes
- Potential drug interactions can occur with beta-blockers, diuretics, digoxin, or monoamine oxidase inhibitors, and tricyclic antidepressants
- Do not exceed the recommended dose
- Adverse events, which occurred at an incidence rate of at least 3% with ProAir HFA, include headache, tachycardia, pain, dizziness, pharyngitis, and rhinitis

Please see Brief Summary of Prescribing Information on next 2 pages.

To learn more about ProAir HFA, visit
ProAirHFA.com/hcp

PROAIR® HFA
(albuterol sulfate) Inhalation Aerosol

The difference is in the design

References: 1. ProAir HFA Prescribing Information. Horsham, PA: Teva Respiratory, LLC; May 2012. **2.** McCabe JC, Koppenhagen F, Blair J, Zeng X-M. ProAir HFA delivers warmer, lower-impact, longer-duration plumes containing higher fine particle dose than Ventolin® HFA. *J Aerosol Med Pulm Drug Deliv.* 2012;25(2):104-109. **3.** Everard ML, Devadason SG, Summers QA, Le Souëf PN. Factors affecting total and "respirable" dose delivered by a salbutamol metered dose inhaler. *Thorax.* 1995;50(7):746-749. **4.** Graham SJ, Ormsby ED, Lovering EG. Single spray drug content in a metered-dose aerosol formulation and a collection scheme for content uniformity. *Pharm Forum.* 1992;18(6):4400-4403.

TEVA Respiratory

BRIEF SUMMARY OF PRESCRIBING INFORMATION FOR PROAIR® HFA (ALBUTEROL SULFATE) INHALATION AEROSOL
For Oral Inhalation Only

SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Bronchospasm

PROAIR HFA Inhalation Aerosol is indicated for the treatment or prevention of bronchospasm in patients 4 years of age and older with reversible obstructive airway disease.

1.2 Exercise-Induced Bronchospasm

PROAIR HFA Inhalation Aerosol is indicated for the prevention of exercise-induced bronchospasm in patients 4 years of age and older.

4 CONTRAINDICATIONS

PROAIR HFA Inhalation Aerosol is contraindicated in patients with a history of hypersensitivity to albuterol and any other PROAIR HFA Inhalation Aerosol components. Rare cases of hypersensitivity reactions, including urticaria, angioedema, and rash have been reported after the use of albuterol sulfate *[see **Warnings and Precautions (5.6)**]*.

5 WARNINGS & PRECAUTIONS

5.1 Paradoxical Bronchospasm

PROAIR HFA Inhalation Aerosol can produce paradoxical bronchospasm that may be life threatening. If paradoxical bronchospasm occurs, PROAIR HFA Inhalation Aerosol should be discontinued immediately and alternative therapy instituted. It should be recognized that paradoxical bronchospasm, when associated with inhaled formulations, frequently occurs with the first use of a new canister.

5.2 Deterioration of Asthma

Asthma may deteriorate acutely over a period of hours or chronically over several days or longer. If the patient needs more doses of PROAIR HFA Inhalation Aerosol than usual, this may be a marker of destabilization of asthma and requires re-evaluation of the patient and treatment regimen, giving special consideration to the possible need for anti-inflammatory treatment, e.g., corticosteroids.

5.3 Use of Anti-inflammatory Agents

The use of beta-adrenergic-agonist bronchodilators alone may not be adequate to control asthma in many patients. Early consideration should be given to adding anti-inflammatory agents, e.g., corticosteroids, to the therapeutic regimen.

5.4 Cardiovascular Effects

PROAIR HFA Inhalation Aerosol, like other beta-adrenergic agonists, can produce clinically significant cardiovascular effects in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of PROAIR HFA Inhalation Aerosol at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Therefore, PROAIR HFA Inhalation Aerosol, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

5.5 Do Not Exceed Recommended Dose

Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs in patients with asthma. The exact cause of death is unknown, but cardiac arrest following an unexpected development of a severe acute asthmatic crisis and subsequent hypoxia is suspected.

5.6 Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions may occur after administration of albuterol sulfate, as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, anaphylaxis, and oropharyngeal edema. The potential for hypersensitivity must be considered in the clinical evaluation of patients who experience immediate hypersensitivity reactions while receiving PROAIR HFA Inhalation Aerosol.

5.7 Coexisting Conditions

PROAIR HFA Inhalation Aerosol, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension; in patients with convulsive disorders, hyperthyroidism, or diabetes mellitus; and in patients who are unusually responsive to sympathomimetic amines. Clinically significant changes in systolic and diastolic blood pressure have been seen in individual patients and could be expected to occur in some patients after use of any beta-adrenergic bronchodilator. Large doses of intravenous albuterol have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

5.8 Hypokalemia

As with other beta-agonists, PROAIR HFA Inhalation Aerosol may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease is usually transient, not requiring supplementation.

6 ADVERSE REACTIONS

Use of PROAIR HFA may be associated with the following:

- Paradoxical bronchospasm *[see **Warnings and Precautions (5.1)**]*
- Cardiovascular Effects *[see **Warnings and Precautions (5.4)**]*
- Immediate hypersensitivity reactions *[see **Warnings and Precautions (5.6)**]*
- Hypokalemia *[see **Warnings and Precautions (5.8)**]*

6.1 Clinical Trials Experience

A total of 1090 subjects were treated with PROAIR HFA Inhalation Aerosol, or with the same formulation of albuterol as in PROAIR HFA Inhalation Aerosol, during the worldwide clinical development program.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adult and Adolescents 12 Years of Age and Older: The adverse reaction information presented in the table below concerning PROAIR HFA Inhalation Aerosol is derived from a 6-week, blinded study which compared PROAIR HFA Inhalation Aerosol (180 mcg four times daily) with a double-blinded matched placebo HFA-Inhalation Aerosol and an evaluator-blinded marketed active comparator HFA-134a albuterol inhaler in 172 asthmatic patients 12 to 76 years of age. The table lists the incidence of all adverse events (whether considered by the investigator drug related or unrelated to drug) from this study which occurred at a rate of 3% or greater in the PROAIR HFA Inhalation Aerosol treatment group and more frequently in the PROAIR HFA Inhalation Aerosol treatment group than in the matched placebo group. Overall, the incidence and nature of the adverse events reported for PROAIR HFA Inhalation Aerosol and the marketed active comparator HFA-134a albuterol inhaler were comparable.

Adverse Experience Incidences (% of Patients) in a Six-Week Clinical Trial*

Body System/Adverse Event (as Preferred Term)		PROAIR HFA Inhalation Aerosol (N = 58)	Marketed active comparator HFA-134a albuterol inhaler (N = 56)	Matched Placebo HFA-134a Inhalation Aerosol (N = 58)
Body as a Whole	Headache	7	5	2
Cardiovascular	Tachycardia	3	2	0
Musculoskeletal	Pain	3	0	0
Nervous System	Dizziness	3	0	0
Respiratory System	Pharyngitis	14	7	9
	Rhinitis	5	4	2

* This table includes all adverse events (whether considered by the investigator drug related or unrelated to drug) which occurred at an incidence rate of at least 3.0% in the PROAIR HFA Inhalation Aerosol group and more frequently in the PROAIR HFA Inhalation Aerosol group than in the placebo HFA Inhalation Aerosol group.

Adverse events reported by less than 3% of the patients receiving PROAIR HFA Inhalation Aerosol but by a greater proportion of PROAIR HFA Inhalation Aerosol patients than the matched placebo patients, which have the potential to be related to PROAIR HFA Inhalation Aerosol, included chest pain, infection, diarrhea, glossitis, accidental injury (nervous system), anxiety, dyspnea, ear disorder, ear pain, and urinary tract infection.

In small cumulative dose studies, tremor, nervousness, and headache were the most frequently occurring adverse events.

Pediatric Patients 4 to 11 Years of Age: Adverse events reported in a 3-week pediatric clinical trial comparing the same formulation of albuterol as in PROAIR HFA Inhalation Aerosol (180 mcg albuterol four times daily) to a matching placebo HFA inhalation aerosol occurred at a low incidence rate (no greater than 2% in the active treatment group) and were similar to those seen in adult and adolescent trials.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of PROAIR HFA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Reports have included rare cases of aggravated bronchospasm, lack of efficacy, asthma exacerbation (reported fatal in one case), muscle cramps, and various oropharyngeal side-effects such as throat irritation, altered taste, glossitis, tongue ulceration, and gagging.

The following adverse events have been observed in postapproval use of inhaled albuterol: urticaria, angioedema, rash, bronchospasm, hoarseness, oropharyngeal edema, and arrhythmias (including atrial fibrillation, supraventricular tachycardia, extrasystoles). In addition, albuterol, like other sympathomimetic agents, can cause adverse reactions such as: angina, hypertension or hypotension, palpitations, central nervous system stimulation, insomnia, headache, nervousness, tremor, muscle cramps, drying or irritation of the oropharynx, hypokalemia, hyperglycemia, and metabolic acidosis.

7 DRUG INTERACTIONS

Other short-acting sympathomimetic aerosol bronchodilators should not be used concomitantly with PROAIR HFA Inhalation Aerosol. If additional adrenergic drugs are to be administered by any route, they should be used with caution to avoid deleterious cardiovascular effects.

7.1 Beta-Blockers

Beta-adrenergic-receptor blocking agents not only block the pulmonary effect of beta-agonists, such as PROAIR HFA Inhalation Aerosol, but may produce severe bronchospasm in asthmatic patients. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-adrenergic-blocking agents in patients with asthma. In this setting, consider cardioselective beta-blockers, although they should be administered with caution.

7.2 Diuretics

The ECG changes and/or hypokalemia which may result from the administration of non-potassium sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of beta-agonists with non-potassium sparing diuretics. Consider monitoring potassium levels.

7.3 Digoxin

Mean decreases of 16% and 22% in serum digoxin levels were demonstrated after single dose intravenous and oral administration of albuterol, respectively, to normal volunteers who had received digoxin for 10 days. The clinical significance of these findings for patients with obstructive airway disease who are receiving albuterol and digoxin on a chronic basis is unclear. Nevertheless, it would be prudent to carefully evaluate the serum digoxin levels in patients who are currently receiving digoxin and PROAIR HFA Inhalation Aerosol.

7.4 Monoamine Oxidase Inhibitors or Tricyclic Antidepressants

PROAIR HFA Inhalation Aerosol should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of albuterol on the cardiovascular system may be potentiated. Consider alternative therapy in patients taking MAO inhibitors or tricyclic antidepressants.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C:

There are no adequate and well-controlled studies of PROAIR HFA Inhalation Aerosol or albuterol sulfate in pregnant women. During worldwide marketing experience, various congenital anomalies, including cleft palate and limb defects, have been reported in the offspring of patients treated with albuterol. Some of the mothers were taking multiple medications during their pregnancies. No consistent pattern of defects can be discerned, and a relationship between albuterol use and congenital anomalies has not been established. Animal reproduction studies in mice and rabbits revealed evidence of teratogenicity. PROAIR HFA Inhalation Aerosol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In a mouse reproduction study, subcutaneously administered albuterol sulfate produced cleft palate formation in 5 of 111 (4.5%) fetuses at an exposure approximately eight-tenths of the maximum recommended human dose (MRHD) for adults on a mg/m^2 basis and in 10 of 108 (9.3%) fetuses at approximately 8 times the MRHD. Similar effects were not observed at approximately one-thirteenth of the MRHD. Cleft palate also occurred in 22 of 72 (30.5%) fetuses from females treated subcutaneously with isoproterenol (positive control).

In a rabbit reproduction study, orally administered albuterol sulfate induced cranioschisis in 7 of 19 fetuses (37%) at approximately 630 times the MRHD.

In a rat reproduction study, an albuterol sulfate/HFA-134a formulation administered by inhalation did not produce any teratogenic effects at exposures approximately 65 times the MRHD *[see **Nonclinical Toxicology (13.2)**]*.

8.2 Labor and Delivery

Because of the potential for beta-agonist interference with uterine contractility, use of PROAIR HFA Inhalation Aerosol for relief of bronchospasm during labor should be restricted to those patients in whom the benefits clearly outweigh the risk. PROAIR HFA Inhalation Aerosol has not been approved for the management of pre-term labor. The benefit:risk ratio when albuterol is administered for tocolysis has not been established. Serious adverse reactions, including pulmonary edema, have been reported during or following treatment of premature labor with $beta_2$-agonists, including albuterol.

8.3 Nursing Mothers

Plasma levels of albuterol sulfate and HFA-134a after inhaled therapeutic doses are very low in humans, but it is not known whether the components of PROAIR HFA Inhalation Aerosol are excreted in human milk.

Caution should be exercised when PROAIR HFA Inhalation Aerosol is administered to a nursing woman. Because of the potential for tumorigenicity shown for albuterol in animal studies and lack of experience with the use of PROAIR HFA Inhalation Aerosol by nursing mothers, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of PROAIR HFA Inhalation Aerosol for the treatment or prevention of bronchospasm in children 12 years of age and older with reversible obstructive airway disease is based on one 6-week clinical trial in 116 patients 12 years of age and older with asthma comparing doses of 180 mcg four times daily with placebo, and one single-dose crossover study comparing doses of 90, 180, and 270 mcg with placebo in 58 patients *[see **Clinical Studies (14.1)**]*. The safety and effectiveness of PROAIR HFA Inhalation Aerosol for treatment of exercise-induced bronchospasm in children 12 years of age and older is based on one single-dose crossover study in 24 adults and adolescents with exercise-induced bronchospasm comparing doses of 180 mcg with placebo *[see **Clinical Studies (14.2)**]*.

The safety of PROAIR HFA Inhalation Aerosol in children 4 to 11 years of age is based on one 3-week clinical trial in 50 patients 4 to 11 years of age with asthma using the same formulation of albuterol as in PROAIR HFA Inhalation Aerosol comparing doses of 180 mcg four times daily with placebo. The effectiveness of PROAIR HFA Inhalation Aerosol in children 4 to 11 years of age is extrapolated from clinical trials in patients 12 years of age and older with asthma and exercise-induced bronchospasm, based on data from a single-dose study comparing the bronchodilatory effect of PROAIR HFA 90 mcg and 180 mcg with placebo in 55 patients with asthma and a 3-week clinical trial using the same formulation of albuterol as in PROAIR HFA Inhalation Aerosol in 95 asthmatic children 4 to 11 years of age comparing a dose of 180 mcg albuterol four times daily with placebo *[see **Clinical Studies (14.1)**]*.

The safety and effectiveness of PROAIR HFA Inhalation Aerosol in pediatric patients below the age of 4 years have not been established.

8.5 Geriatric Use

Clinical studies of PROAIR HFA Inhalation Aerosol did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy *[see **Warnings and Precautions (5.4, 5.7)**]*.

All $beta_2$-adrenergic agonists, including albuterol, are known to be substantially excreted by the kidney, and the risk of toxic reactions may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

10 OVERDOSAGE

The expected symptoms with overdosage are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the symptoms listed under ADVERSE REACTIONS, e.g., seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats per minute, arrhythmias, nervousness, headache, tremor, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, and insomnia.

Hypokalemia may also occur. As with all sympathomimetic medications, cardiac arrest and even death may be associated with abuse of PROAIR HFA Inhalation Aerosol.

Treatment consists of discontinuation of PROAIR HFA Inhalation Aerosol together with appropriate symptomatic therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for overdosage of PROAIR HFA Inhalation Aerosol.

The oral median lethal dose of albuterol sulfate in mice is greater than 2,000 mg/kg (approximately 6,800 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis and approximately 3,200 times the maximum recommended daily inhalation dose for children on a mg/m^2 basis). In mature rats, the subcutaneous median lethal dose of albuterol sulfate is approximately 450 mg/kg (approximately 3,000 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis and approximately 1,400 times the maximum recommended daily inhalation dose for children on a mg/m^2 basis). In young rats, the subcutaneous median lethal dose is approximately 2,000 mg/kg (approximately 14,000 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis and approximately 6,400 times the maximum recommended daily inhalation dose for children on a mg/m^2 basis). The inhalation median lethal dose has not been determined in animals.

Mktd by: Teva Respiratory, LLC
Horsham, PA 19044

Mfd by: IVAX Pharmaceuticals Ireland
Waterford, Ireland

Manufactured In Ireland Rev 05/12

PA0512BS-A

Valerie DeBenedette, Contributing Editor

The patient-centered medical home

Your role will grow as this healthcare model evolves

Whether they are called patient-centered medical homes (PCMHs), medical homes, or anything else, their purpose is to provide patients with comprehensive, integrated, efficient, and effective primary healthcare. Along with other healthcare professionals, pharmacists are learning their roles in this still-developing model of healthcare delivery.

Definitions

PCMH definitions vary, but most keep the main points intact.

The National Committee for Quality Assurance states that a PCMH "is a healthcare setting that facilitates partnerships between individual patients, their personal physicians, and when appropriate, the patient's family."

The Patient-Centered Primary Care Collaborative calls the PCMH "a model or philosophy of primary care that is patient-centered, comprehensive, team-based, coordinated, accessible, and focused on quality and safety."

According to the American College of Physicians, a PCMH should be using information technology, health information exchange, and other means to ensure that patients receive healthcare that matches their language and cultural needs, when and where they need it.

The U.S. Department of Veterans Affairs calls the team-based concept it uses at some VA facilities PACT, which stands for "patient-aligned care team."

Development of an idea

The concept of a team-based primary care delivery system was first used in the late 1960s by the American Academy of Pediatrics to describe a system for keeping track of the medical care of a child in a family-centered, comprehensive, and continuous way. Since then, the concept and its definitions have been refined by the groups already mentioned, as well by as the American Academy of Family Physicians and the American Osteopathic Association.

Several organizations are dedicated to advancing the idea of medical homes, including the Patient-Centered Primary Care Collaborative. The organization has a membership of more than 1,000 medical home stakeholders and supporters, according to information posted at its website.

In some PCMH models, care may be coordinated by a physician assistant or nurse practitioner instead of by a physician. In addition to these three healthcare professionals, healthcare teams can include nurses, social workers, psychologists, and pharmacists.

Growing awareness

Although the terms "medical home" and "PCMH" may be used informally to describe any comprehensive healthcare practice, there is an accrediting program run by the Accreditation Association for Ambulatory Health Care. The National Committee for Quality Assurance has created a set of voluntary standards for the recognition of medical practices as PCMHs.

"[Patient-centered medical home] is a buzzword right now. I think pharmacists know the terminology but may not understand the requirements or the need for patient-centered medical homes," said Jean Moon, PharmD, BCACP, assistant professor in the Department of Pharmaceutical Care and Health Systems at the University of Minnesota College of Pharmacy in Minneapolis. "The pharmacists' role in this is just being discovered and being studied in the literature."


Jean Moon

She continued, "The everyday pharmacist may not know everything about patient-centered medical homes, but they understand the overall concept."

In addition to her academic work, Moon works part-time at Broadway Family Medicine, a PCMH in north Minneapolis. There she consults with patients, reconciles medication lists, and works to resolve medication-related issues.

Numbers TBA

The number of PCMHs in the United States is definitely growing, but it is difficult to get a handle on how many already exist, Moon said.

One count conducted in Minnesota started out with about 160 PCMHs, but by the time the study was published, the list included around 200, she said. These numbers should level off as the medical practices and community health clinics that have decided to seek accreditation complete the process.

The number of pharmacists employed by PCMHs or consulting with them on a regular basis is also not known, Moon said. The ideal size and makeup of the staff in a PCMH is still being determined, she added.

"How many part-time pharmacists are needed in a certain health system? How do we optimize the time they are there?" she asked, citing areas that need more study.

PCMHs generally include pharmacists as a formal part of the healthcare team, sometimes as outside consultants, but also as full-time or part-time employees. Staff pharmacists may hold face-to-face consultations with patients who have complicated medication regimens, several coexisting conditions, or conditions that fail to stabilize or improve despite medication therapy. Other medical homes refer such patients to community pharmacists for these consultations.

MTM is key

Medication therapy management (MTM) is a key element of a PCMH, according to Hayden B. Bosworth, PhD, professor in the Department of Medicine and the Department of Psychiatry and Behavioral Sciences in the School of Medicine and School of Nursing at Duke University in Durham, N.C.


Hayden Bosworth

"It makes sense that the more complex the medication regimen, the more you need a pharmacist," Bosworth said. Some physicians are comfortable working on medication issues with patients who are on several prescriptions or who need complicated drug regimens, but studies have shown that teams that work with a pharmacist are more effective than those that do not, he said.

Patients who are having adherence problems also benefit from meeting with a pharmacist, he said. "We do a terrible job of recognizing medication adherence issues," Bosworth said. When increased hospitalizations and wasted medications are factored in, noncompliance to medication regimens may cost nearly $290 billion annually in the United States.

"We need to ensure — given the healthcare problems that we are facing in our society — that we figure out better ways of utilizing the role of pharmacists," Bosworth said.

Managing medications helps to keep patients out of the hospital, which is a cost-effective treatment goal of the PCMH. Medication management conducted by a pharmacist can be more productive for those patients who need more

Continued on pg. 38

The patient-centered medical home

Continued from pg. 37

time and attention than they can obtain from their primary healthcare professionals.

Which patients benefit?

How to determine which patients benefit most from working directly with a pharmacist is still not well understood, Moon said.

One good indicator of the need for a pharmacist consultation is the number of prescriptions the patient is filling; the more medications the patient takes, the greater the possibility for drug interactions, medication errors, side effect issues, and adherence problems, she noted. But other predictors also need to be evaluated, she said.

One strategy to determine whether patients should meet with a pharmacist is to earmark those who are taking 10 or more medications, Moon said. However, at a busy PCMH such as Broadway Family Medicine, there may be as many as 60 patients coming in each day who meet that criterion.

"There is no way that I can see 60 patients a day," she said.

A better indicator may need to be developed than simply the number of prescribed medications.

Recent hospitalizations or visits to the emergency room also may be useful indicators to help determine which patients need to consult with a pharmacist, she added.

Diabetes and hypertension

Many studies of MTM have centered on patients with diabetes, Moon said. Studies have shown that patients who receive a consultation do a better job of managing their conditions and making changes in their lifestyles to help control blood glucose levels.

In a review of studies of team-model practices that looked at patients with hypertension, teams of pharmacists and nurses have been found to help patients control their blood pressure, Bosworth reported.

Reimbursement

As the PCMH model expands in numbers and scope, the issue arises of how pharmacists will be paid for their work.

Reimbursement or payment for the work of pharmacists and other professionals within a PCMH can be accomplished in several ways. One is a fee-for-service model, said Bosworth, with the pharmacist being paid for each consultation with a patient. This type of model is commonly used.

Other payment models include a care-coordination payment system and a performance-based component. The care-coordination payment approach covers anything that falls outside a face-to-face visit. The performance-based component recognizes when the goal of the service has been achieved.

All three types of payment or reimbursement models can be blended, according to the Patient-Centered Primary Care Collaborative.

More to learn

As the healthcare system in the United States reforms and changes, PCMHs and similar practice types continue to be studied and evaluated. Research is underway, and studies are being published that evaluate the effectiveness and efficiency of pharmacists and MTM within a medical home, Moon said. "I think there is still a lot to learn about patient-centered medical homes,"she added.

"At end of day, the goal is to achieve coordination of care," Bosworth said. "I don't think the potential of what the pharmacist can do [within a PCMH] has been achieved." DT

Valerie DeBenedette *is a medical news writer in Putnam, N.Y.*

Resources on the PCMH

For more information, check out these websites:

American College of Clinical Pharmacy

"The Patient-Centered Medical Home: Integrating Comprehensive Medication Management to Optimize Patient Outcomes: Resource Guide"
Available at *http://bit.ly/ACCPguide*

Pennsylvania Pharmacists Association

"The Pharmacists' Role in the Patient-Centered Medical Home"
Available at *http://bit.ly/PharmRole*

The American College of Physicians

Patient-Centered Medical Home page
http://bit.ly/AmColPhysPCMH

The Patient-Centered Primary Care Collaborative

http://www.pcpcc.org/

U.S. Department of Health and Human Services

Agency for Healthcare Research and Quality
The Patient Centered Medical Home Resource Center
http://bit.ly/PCMHrc

Mark P. Walberg, PharmD, PhD

GBS risk after influenza vaccination

Guillain-Barré syndrome (GBS) is an immune-mediated flaccid paralysis that can range from muscle weakness and tingling to respiratory paralysis requiring prolonged respiratory support and ventilation. Overall, GBS is a rare disease, with annual incidence averaging one to two cases per 100,000 individuals.[1]

Origins

This autoimmune disease is thought to be the result of molecular mimicry between gangliosides (a type of glycolipid found in cell membranes, with high concentrations in nervous system tissues) and lipopolysaccharides of bacteria and viruses.[1] Essentially, antibodies formed against an antigenic component of a pathogen also have affinity for a component of the host's cell membrane, such as a glycolipid.

Campylobacter jejuni infections, a common cause of gastrointestinal illness, precede roughly one-third of all GBS cases.[1] GBS risk is estimated to be over 38 times greater for those inviduals recently infected by *C. jejuni* and over 18 times greater for those with influenza and influenza-like illnesses.[2]

An increased GBS rate was observed during the 1976 swine flu vaccination campaign, with approximately one additional case of GBS per 100,000 individuals vaccinated above background rates (532 cases in 45 million vaccinated persons).[3]

Studies

Since 1976, the rate of GBS attributed to influenza vaccination has been approximately one additional case per one million vaccinated persons. Numerous studies have been conducted over single and multiple influenza seasons and have examined their corresponding vaccines. A thorough review of the topic can be found in a 2012 publication from the Institute of Medicine, which concluded that there was sufficient evidence to reject an association between influenza vaccination and GBS.[4]

A 2013 study by Baxter, et.al, further supported the lack of association between GBS and several vaccines, including influenza. This study spanned 13 years and included almost 33 million patient-years. The background incidence of GBS was 1.27 per 100,000 individuals, matching

Continued on pg. 55

NEW DRUG REVIEW Kathryn Wheeler, PharmD

New SERM approved for dyspareunia

On February 26, 2013, FDA approved ospemifene (Osphena, Shionogi Inc.) for the treatment of moderate-to-severe dyspareunia resulting from vulvar and vaginal atrophy associated with menopause. Estrogen levels decline during menopause, resulting in a thinning and drying of vaginal tissues. This atrophy can cause a woman to experience pain during intercourse (dyspareunia).

An estrogen receptor agonist, ospemifene counteracts the effects of declining estrogen hormones on vaginal tissue, thereby reducing pain during intercourse. Previous treatment options for menopause-related dyspareunia include lubricating vaginal products and local and systemic estrogen therapy. While ospemifene is not a panacea, it is an additional tool.

Efficacy

FDA approved ospemifene on the basis of results from two randomized, double-blind, placebo-controlled, parallel-group 12-week trials. The first trial studied the effects of ospemifene 30 mg, 60 mg, and placebo in women 41 to 81 years of age, who had ≤=5% superficial cells on baseline vaginal smear, vaginal pH>5.0 (both measurable signs of atrophy), and one or more moderate-to-severe vaginal symptoms (vaginal dryness, itching, irritation, or dyspareunia) noted by participants as most troublesome. At week 12, participants were assessed for improvement in the symptoms and changes from baseline for vaginal pH and percentage of superficial cells.

The second trial was similarly structured. Ages ranged from 49 to 79 years (mean of 59 years). However, participants identified either moderate-to-severe vaginal dryness or dyspareunia as their most bothersome symptom and were administered either 60 mg of ospemifene or placebo.

Results from an intention-to-treat analysis of both trials indicate statistically significant increases in the percentage of superficial cells, as well as decreases in vaginal pH, in women treated with ospemiphene compared to placebo (P=<.0001). In both trials, women taking ospemifene experienced improvement in moderate-to-severe dyspareunia (P=.0012 in the first trial, P=<.0001 in the second trial) compared to women in the placebo group.

Safety

The safety of ospemifene was evaluated with a 52-week randomized, double-blind, placebo-controlled, long-term safety study comparing ospemifene 30 mg or 60 mg to placebo in 426 participants with an intact uterus who ranged in age from 49 to 79 years.

Ospemifene was generally well tolerated and no clinically significant adverse endometrial changes were observed. However, women in the treatment groups demonstrated a greater incidence of endometrial thickening. Adverse effects demonstrated most often in trials included hot flashes, excessive sweating, muscle spasms, and vaginal or genital discharge. Most participants reported that hot flashes were the most significant adverse effect.

Ospemifene carries a boxed warning for increased risk of endometrial cancer and cardiovascular disorders. At the endometrium, ospemifene behaves as an agonist, stimulating the proliferation of tissue. In post-menopausal women, any bleeding should be investigated as a possible sign of endometrial cancer or its precursor, endometrial hyperplasia. Ospemifene has demonstrated increased incidence of hemorrhagic and thromboembolic strokes (0.72 and 1.45 per 1,000 women respectively) compared to placebo (1.04 and 0 per 1,000 women respectively) in trials. The incidence of DVT is increased with ospemifene 60 mg compared to placebo (1.45 vs. 1.04 per 1,000 women). This finding led to the recommendation for discontinuation of ospemiphene 4 to 6 weeks before surgery.

Ospemifene has not been well studied in women with breast cancer and should therefore be avoided in women with breast cancer or a history of breast cancer. It has not been studied in comparison to estrogens or in combination with other hormonal therapies for menopausal symptoms. It should be taken for the shortest duration necessary to alleviate troublesome symptoms associated with menopause.

Dosage

Ospemifene is approved for use as a once-daily oral 60-mg tablet. The manufacturer recommends that it be taken with food to increase its bioavailability. No dose adjustment is necessary for renal impairment. Ospemifene has not been studied in women with severe liver disease and should be avoided in women with Child-Pugh class C hepatic impairment. Ospemifene is primarily metabolized by CYP3A4 and CYP2C9 and to a lesser degree CYP2C19. Coadministration with inhibitors and inducers of these enzymes can alter blood levels of ospemifene. Ospemifene was not shown to significantly alter the pharmacokinetics of a single dose of warfarin. However, no study of the effects of ongoing co-administration of ospemifene and warfarin has been performed. Ospemifene is highly plasma protein-bound (>99%). Although not studied, it is expected that ospemifene can increase the free concentration of other highly protein-bound drugs. DT

Kathryn Wheeler, PharmD, *is assistant clinical professor of pharmacy practice, University of Connecticut School of Pharmacy, Storrs, Conn.*

ANTICOAGULATION THERAPIES Anna D. Garrett, PharmD, BCPS

Aspirin not needed with anticoagulation/ clopidogrel after MI, PCI in AF

A Danish study of over 12,000 patients with atrial fibrillation (AF) who had a myocardial infarction (MI) or percutaneous coronary intervention (PCI) suggests that the addition of one antiplatelet agent to oral anticoagulation is sufficient. The review also found that the best agent to add is clopidogrel (vs. aspirin).

The study used nationwide registries to track 12,165 patients with AF who were hospitalized for MI or PCI; about 61% were men, and the mean age was 75. Nearly two-thirds were treated with multiple antithrombotic drugs at baseline, and 38.3% received oral anticoagulation therapy.

Triple antithrombotic therapy is commonly used in patients with multiple indications for antithrombotic therapy. The data suggest that replacing triple therapy regimens with oral anticoagulation and clopidogrel will carry a lower risk of bleeding and no additional risk of recurrent thrombotic events, the authors indicated.

An accompanying editorial cautioned against extrapolating these results to the newer target-specific anticoagulants, citing that adding dual antiplatelet agents to the new agents would be likely to cause more bleeding than benefit.

Sources: Lamberts M, Gislason GH, Olesen JB, et al. Oral anticoagulation and antiplatelets in atrial fibrillation patients after myocardial infarction and coronary intervention. J Am Coll Cardiol. *2013;Epub ahead of print. Markowitz SM. Antithrombotic regimens in patients with atrial fibrillation and coronary disease: Optimizing efficacy and safety [editorial].* J Am Coll Cardiol. *2013;Epub ahead of print. June 4, 2013 in the Journal of the American College of Cardiology.*

Smoking increases risk of VTE during postoperative period

Evidence about the effect of smoking on venous thromboembolism (VTE) risk is limited and inconsistent. A subanalysis of the Million Women Study (U.K.) examined the incidence of VTE in relation to smoking habits, both in the absence of surgery and in the first 12 postoperative weeks.

Of the women included in this study, 4,630 (mean age 56) were admitted to the hospital for or died of VTE. Current smokers had a significantly increased incidence of VTE compared with those who never smoked (adjusted RR=1.38), with significantly greater risks in heavier (>15 cigarettes per day) vs. lighter smokers.

Current smokers were also more likely to have surgery than those who never smoked (RR=1.12), 95% CI, 1.12-1.13). Among women who had surgery, the incidence of VTE in the first 12 postoperative weeks was significantly greater in current smokers than for those who never smoked (RR=1.16).

Smoking increases the overall risk of VTE whether or not the patient is postop. However, the risk is greater in the postoperative period. Therefore, smoking should be considered in the assessment of VTE risk in patients undergoing surgery.

Source: Sweetland S, Parkin L, Balkwill A, et al. Smoking, surgery, and venous thromboembolism risk in women. Circulation. *2013;127:1276–1282.*

Newer generation heart valve may allow for lower intensity anticoagulation

Researchers recently presented findings of a study using low-dose warfarin to prevent complications with a newer-generation mechanical aortic valve.

The interim results reflect assessment of 375 patients whose preoperative risk factors for thromboembolism required aortic valve replacement and who met high-risk criteria that included chronic atrial fibrillation, left ventricular ejection fraction <30%, ventricular aneurysm, an enlarged left atrium of >50 mm in diameter, and spontaneous echo contrast in the left atrium.

The patients were randomized to receive either lower-dose warfarin (n=190; INR=1.5-2.0) or to continue standard-dose warfarin (INR=2.0-3.0) for three months following mechanical AVR with the On-X mechanical valve. All the patients received 81-mg aspirin daily, and INR was adjusted according to home monitoring. Mean age was 55.2, and 79% were male.

Follow-up averaged 3.42 years. Patients in the low-dose warfarin group had a mean INR of 1.89, compared with 2.50 in the standard-dose group. The low-dose group had significantly lower major and minor bleeding event rates. There were no significant differences between the two groups in terms of stroke, transient ischemic attack, or total neurological events and no significant differences in all-cause mortality. The study is ongoing.

Source: Puskas JD, Nichols D, Gerdisch M, et al. Reduced anticoagulation after mechanical aortic valve replacement: Interim results from the PROACT randomized FDA IDE trial. American Association for Thoracic Surgery 2013 Annual Meeting. May 6, 2013; Minneapolis, MN. Abstract 1. DT

Anna D. Garrett *is a clinical pharmacist and president of Dr. Anna Garrett (www.drannagarrett.com). Her mission is to help women in midlife maximize their mojo! Contact her at info@drannagarrett.com.*

CPE CREDIT: 2.0

EARN CE CREDIT FOR THIS ACTIVITY AT WWW.DRUGTOPICS.COM

EDUCATIONAL OBJECTIVES

Goal: To discuss background information, including pathophysiology, guideline recommendations for screening and treatment, and patient self-care, as related to the care of patients with osteoporosis.

After participating in this activity, pharmacists will be able to:

- **Explain the bone remodeling process and pathophysiology of osteoporosis**
- **Identify osteoporosis risk factors, including medications that can adversely affect bone health**
- **Distinguish between osteoporosis and osteopenia using dual-energy x-ray absorptiometry (DXA) results and the FRAX assessment tool**
- **Utilize current osteoporosis guidelines to recommend osteoporosis screening and initiation of therapy**
- **Discuss recent developments on the cardiovascular risk associated with calcium and vitamin D supplementation**

The University of Connecticut School of Pharmacy is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

Pharmacists are eligible to participate in the application-based activity, and will receive up to 0.2 CEUs (2 contact hours) for completing the activity, passing the quiz with a grade of 70% or better, and completing an online evaluation. Statements of credit are available via the online system.

ACPE #0009-9999-13-072-H01-P

Grant Funding: This activity is supported by an educational donation provided by Amgen.

Activity Fee: There is no fee for these activities.

Initial release date: 9/10/2013
Expiration date: 9/10/2015

To obtain immediate credit, take the test online at *www.drugtopics.com/cpe.* Just click on the link in the yellow box under **Free CPE Activities,** which will take you to the CPE site. For first-time users, please complete the registration page. For those already registered, log in, find, and click on this lesson. Test results will be displayed immediately. Complete the evaluation form and *Drug Topics* will be electronically uploading your CPE credit to CPE Monitor via your NABP e-profile ID. You should be able to view your credits within a two-week period of completing the evaluation.

For questions concerning the online CPE activities, e-mail: *cpehelp@advanstar.com.*

Drug Topics & University of Connecticut School of Pharmacy
Continuing Education
AN ONGOING CE PROGRAM OF THE UNIVERSITY OF CONNECTICUT SCHOOL OF PHARMACY AND *DRUG TOPICS*

MTM considerations in osteoporosis care

Pathophysiology, screening, and prevention strategies

Marissa C. Salvo, PharmD
ASSISTANT CLINICAL PROFESSOR, UNIVERSITY OF CONNECTICUT SCHOOL OF PHARMACY, STORRS, CONN.

Montanna Paulhus, PharmD Candidate 2014
UNIVERSITY OF CONNECTICUT SCHOOL OF PHARMACY, STORRS, CONN.

Mario Ferreira, PharmD Candidate 2014
UNIVERSITY OF CONNECTICUT SCHOOL OF PHARMACY, STORRS, CONN.

Abstract

The number of individuals with osteoporosis is set to rise due to an increasing older adult population. Pharmacists are highly accessible and well trained to provide medication therapy management services for patients with osteoporosis. It is therefore important for pharmacists to review the pathophysiology of and risk factors for osteoporosis. Pharmacists also need to stay abreast of updates regarding osteoporosis care, such as clinical evidence and practice guidelines. In doing so, they can recommend screening, treatment, as necessary, and patient self-care.

Faculty: Marissa C. Salvo, PharmD; Montanna Paulhus, PharmD Candidate; Mario Ferreira, PharmD Candidate
Dr. Salvo is an assistant clinical professor, University of Connecticut School of Pharmacy, Storrs, Conn., and clinical pharmacist, Community Health Center, Inc.

Faculty Disclosure: Dr. Salvo, Ms. Paulhus, and Mr. Ferreira have no actual or potential conflict of interest associated with this article.

Disclosure of Discussions of Off-Label and Investigational Uses of Drugs: This activity may contain discussion of unlabeled/unapproved use of drugs. The content and views presented in this educational program are those of the faculty and do not necessarily represent those of *Drug Topics* or Univeersity of Connecticut School of Pharmacy. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.

IMAGE: THINKSTOCK / ISTOCKPHOTO

Editor's note: This is the first article in a two-part series. Next month, we will cover current issues for prevention and treatment of osteoporosis.

Osteoporosis, a systemic skeletal disease, is characterized by low bone mass, deterioration of bone tissue, and disruption of bone architecture, which compromises bone strength and increases the risk for fractures.[1] Similar to some other chronic diseases, osteoporosis is an asymptomatic disease, often undiagnosed until complications arise or screening occurs. In the United States, approximately 10 million individuals older than age 50 currently have diagnosed osteoporosis. Another 34 million have osteopenia, which may progress to osteoporosis.[2]

The primary functions of the skeletal system are structural and metabolic. Structurally, the skeletal system supports and protects the organ systems of the body; while metabolically, it stores calcium, phosphorus, and magnesium. Both structural and metabolic functions have a role in the bone modeling and remodeling process, which is vital for bone health.[3,4]

Highly regulated specialized cells, known as osteoblasts and osteoclasts, carry out the modeling and remodeling of bones through the use of signaling pathways.[4] Osteoclasts break down the mineral and collagen matrix in a process known as bone resorption. This process facilitates the retrieval of stored minerals by dissolving the bone and recycling the recovered minerals for either structural or metabolic purposes.[4]

In comparison to osteoclasts, osteoblasts create the collagen matrix that serves as the foundation for bone. The collagen matrix, consisting of calcium, phosphorus, and magnesium, increases bone strength. Nearly 60% of the body's magnesium and 80% of the body's phosphorus stores are found within the bone tissue. Osteoblasts form the collagen matrix in a layered fashion to provide additional strength to the matrix. Osteoblasts incorporated into the collagen matrix during formation are known as osteocytes. Osteocytes, the most prevalent cell found within bone, form elaborate networks that assist in bone response to mechanical force.[4]

Bone modeling and remodeling is a dynamic process in which old bone is resorbed by osteoclasts and new bone is formed by osteoblasts. The bone remodeling cycle varies in length with osteoclast resorption lasting 2 to 4 weeks and osteoblast formation averaging 5 weeks.[3] The balanced process of bone formation and removal involves communication of the osteoblasts and osteoclasts in response to external and internal stimuli, such as changes in physical activity (weight bearing exercise) and chemical mediators (serum calcium levels). Bone disease, including osteopenia and osteoporosis, occurs when there is an imbalance between osteoclasts and osteoblasts resulting in a favoring of bone destruction over bone formation.[4]

It is projected that by 2020, 1 in 2 U.S. citizens over the age of 50 will have or be at risk of developing osteoporosis of the hip.

Parathyroid hormone (PTH), calcitriol, and calcitonin are considered the 3 primary chemical mediators that regulate calcium. PTH serves a duel function by not only stimulating the kidneys to conserve calcium, but also by stimulating calcitriol production to enhance calcium and phosphorus absorption in the gastrointestinal tract, thus regulating serum calcium levels. Calcitriol is a mediator for calcium regulation and is derived from vitamin D; hence, adequate consumption is crucial. Calcitonin prevents bone breakdown by inactivating osteoblasts.

The male and female sex hormones, testosterone and estrogen, respectively, also influence bone health. In males, testosterone is converted into estrogen. Continual production of testosterone throughout a man's lifespan results in higher serum estrogen concentrations in older adult men than in postmenopausal women, in whom estrogen production declines following menopause. Estrogen production is critical to bone health, as estrogen suppresses osteoclast activation, influences osteoblast formation by stimulating proliferation and decreasing apoptosis, and decreases production of receptor activator of nuclear factor kappa B ligand (RANKL).[3]

The RANKL-RANK pathway is a vital component of osteoclast formation and activation. Interaction of RANKL with RANK on osteoclasts prolongs cell survival by decreasing apoptosis. Estrogen decreases the sensitivity of RANKL to osteoclast precursors resulting in decreased bone resorption. Osteoprotegerin, another mediator, is mainly produced by osteoblasts and serves as a decoy receptor for RANKL promoting osteocyte apoptosis.[3] Hence decreased estrogen production postmenopause is associated with decreased bone mineral density (BMD) and an increased risk of osteoporosis and fracture(s).

Each year an estimated 1.5 million persons suffer an osteoporotic-related fracture, an event that often leads to deterioration in both physical and mental health. For U.S. adults over the age of 50, 40% of Caucasian women will experience a hip, spine, or wrist fracture during the remainder of their lives, while only 13% of Caucasian men will suffer a similar fate.[2] Mortality rates post-fracture are lower for women than for men despite higher prevalence, due in part to the older age at which men suffer from fractures and differences in medical care. Individuals who suffer an osteoporotic-related fracture are often burdened by significant pain and height loss, and may lose the ability to complete activities of daily living. Furthermore, the psychological consequences of fractures may negatively impact self-esteem, body image, and mood.[4]

Heathcare costs for osteoporotic-related fracture management and treatment are expensive. Studies show that in 2002 annual direct care expenditures ranged from $12 to $18 billion, with indirect costs, such as lost productivity,

TABLE 1

RISK FACTORS FOR OSTEOPOROSIS

Nonmodifiable risk factors	Modifiable risk factors
Age (>50 yrs)	**Nutritional status**
Sex (female > male)	**Vitamin D**
Menopause	(RDA age 51–70 yrs = 400 IU)
Family history of osteoporosis	(RDA age >70 yrs = 600 IU)
History of fractures	**Calcium**
Body weight (<57.5 kg)	(RDA age 19–50 yrs = 1000 mg)
BMI (<21 kg/m^2)	(RDA age >51 yrs = 1,200 mg)
	Phosphate
	(RDA age >19 yrs = 700 mg)
	Magnesium
	(RDA men age >31 yrs = 420 mg)
	(RDA female age >31 yrs = 320 mg)
	Lifestyle
	Limited physical activity
	Alcohol use
	Current smoker
	Medications
	Aromatase inhibitors
	Anticonvulsants
	Androgen deprivation therapy
	Glucocorticoids
	Proton pump inhibitors
	Selective serotonin reuptake inhibitors
	Thiazolidinediones
	Levothyroxine

Abbreviations: BMI, body mass index; RDA, recommended daily allowance; IU, international units

Source: Ref 1,4–6

adding billions of dollars to this figure. Costs could double or triple in the coming decades. It is projected that by 2020, 1 in 2 U.S. citizens over the age of 50 will have or be at risk of developing osteoporosis of the hip, and even more will be at risk of developing osteoporosis at any site in the skeleton.[4] With these staggering figures in mind, pharmacists are in a key position to identify individuals with risk factors for osteoporosis and recommend or complete BMD testing.

Risk factors

Osteoporosis risk factors broadly include environmental, familial, and medication-related categories and can be subdivided into those that are modifiable and nonmodifiable, as outlined in **Table 1**.[4-6] Age is a significant nonmodifiable risk factor for osteoporosis, with the risk of fracture doubling every 7 to 8 years in persons over the age of 50.[5] Women are especially susceptible to osteoporosis compared to men due to decreasing estrogen levels postmenopause. On average, women experience accelerated bone loss of 2% for 2 to 3 years prior to menopause and for 3 to 4 years postmenopause. After this time, bone loss for women decreases on average by 1% to 1.5% annually. Additionally, peak BMD is influenced by family history; approximately 80% of variability can be attributed to genetic factors. Lower BMD trends have been noted in women who have first-degree relatives such as a mother or sister with osteoporosis. A history of fracture(s) must also be considered when determining an individual's risk for osteoporosis. Menopausal women with a history of fracture(s) are at a 2-fold increase for experiencing another fracture, likely from decreased BMD.[5]

Modifiable risk factors for the development of osteoporosis include lifestyle, nutritional status, and the use of certain prescription medications. Body weight, specifically thinness, and low body mass index (BMI) values are important factors when evaluating the risk for osteoporosis. Thresholds for body weight and BMI are 57.5 kg and 21 kg/m^2, respectively; below these numbers the risk increases for low BMD and fracture risk, especially for elderly women.[5]

Weight-bearing physical activity preserves bone mass, which in turn generates growth and maintenance of the skeleton.[4] Increasing physical activity in the form of muscle strengthening and balance exercises reduces the risk of falls and fall-related injuries by 75%.[5] Pharmacists can suggest that patients increase daily physical activity through simple interventions such as parking further away from the desired location and walking or climbing the stairs instead of taking the elevator. For individuals who are relatively inactive, 5 to 10 minutes of activity per day is recommended; whereas, individuals who are more active can increase activity levels to 20 to 30 minutes per day. Physical activity preferably should occur on all days of the week. Length of activity should not increase by more than 10% each week, and it is always advisable to have individuals consult with their physician prior to starting strenuous physical activity.[4]

Both smoking and alcohol consumption have an impact on the risk for osteoporosis. Smokers tend to have lower bone mass when compared to nonsmokers.[5] Although the exact mechanism is unknown, smoking is believed to impair calcium absorption and lower estrogen levels. Women should limit alcohol to no more than 2 drinks (one drink equals 12 ounces beer, 4 ounces wine, or 1 ounce of liquor) per day.[5] Pharmacists may assist individuals by providing patient education, developing a plan to institute healthy lifestyle changes, and motivating patients to make the desired changes.

Inadequate nutrition affects calcium and vitamin D consumption in addition to other required minerals for bone development and maintenance. Based on data from the National Health and Nutrition Examination Survey 1999 to 2000, women age 40 years and older have an average dietary calcium intake of between 660 mg and 744 mg daily.[7] With this in mind, an additional 300 to 600 mg per day is needed for most women to reach

the daily recommended value of 1,000 mg to 1,200 mg. In addition, vitamin D is essential for intestinal absorption of calcium; yet similar to calcium, dietary intake is often low in adults.[5]

Some prescription medications may adversely influence bone health and are addressed in the following discussion. The current belief is that bone loss is greater when taking higher doses for longer periods of time. When possible, the lowest effective dose of medication(s) should be utilized to reduce bone loss.

Drug-induced causes

Glucocorticoids, such as prednisone, impact bone formation by impairing osteoblast function, and with use over time weaken the skeleton. Roughly 20% to 30% of individuals on oral glucocorticoids will experience a fracture due to impaired bone turnover. Additionally, oral glucocorticoids are responsible for commonly causing drug-induced osteoporosis.[4,6] The National Osteoporosis Foundation (NOF) suggests that an increased risk is associated with daily oral prednisone doses of ≥5 mg or equivalent of another glucocorticoid taken for 3 or more months.[1] Both inhaled and topical forms of glucocorticoids pose a risk, although to a lesser extent than oral forms, for drug-induced osteoporosis because of limited systemic absorption.[4,6]

Estimates show that approximately 25% of patients are overtreated for hypothyroidism, resulting in depressed levels of thyroid stimulating hormone (TSH). TSH may play a direct role with inhibition of bone resorption; hence, supratherapeutic doses of levothyroxine, the cornerstone for treatment of hypothyroidism, may result in bone loss in predisposed individuals such as postmenopausal women. Supratherapeutic doses may also result in subclinical hyperthyroidism; its effects on the skeletal system also depend on age, sex, and duration of treatment.[6]

The mechanism of action for proton pump inhibitors (PPIs) involves inhibition of gastric acid production and secretion, which may impair calcium absorption. Impaired absorption of calcium, a relatively insoluble mineral, may increase bone resorption.[8] The risk for fractures is dependent on duration of therapy and dose.[6] In 2011 the FDA stated that short-term use and low doses of PPIs are unlikely to cause fractures. Individuals at greatest risk for osteoporotic-related fractures are those who use PPIs for more than 1 year or at high doses. Despite the risk, routine BMD screening is not recommended for patients on long-term PPI therapy unless additional risk factors exist.[9] However, the increased risk of fractures is considered reversible after PPI withdrawal for more than 1 year.[6]

Thiazolidinediones (TZDs), pioglitazone and rosiglitazone, have the ability to alter bone metabolism by not only increasing bone resorption through osteoclast stimulation but also by decreasing the formation of osteoblasts. The risk for fractures increases 4-fold for postmenopausal women using a TZD. Within 12 to 18 months of treatment with TZDs, fracture risk is significant for patients with either established osteoporosis or at high risk for osteoporosis.[6,10]

Bone loss is greater when taking higher doses for longer periods of time.

Aromatase inhibitors, such as letrozole and anastrozole, induce bone loss by inhibiting the conversion of androgens to estrogens in peripheral tissues. The reduction of estrogen in peripheral tissue results in increased bone turnover rate by osteoclasts, leading to decreased BMD. Unfortunately, withdrawal of aromatase inhibitors results in only a partial recovery of BMD. The osteoporotic effects of the aromatase inhibitors are most prevalent in early menopause and inversely related to baseline BMD and serum estradiol concentrations.[6]

With use of androgen deprivation therapy (bicalutamide and leuprorelin), both testosterone and estradiol serum levels are reduced, resulting in increased BMD loss due to increased bone turnover. Factors such as duration of therapy and patient age correlate with increased risk of fracture. It is estimated that fracture risk increases by 40% to 50% in individuals using androgen deprivation therapy for 12 months.[6]

The mechanism through which bone metabolism is altered by anticonvulsants is not fully understood. All anticonvulsants are known to increase metabolism of vitamin D, which decreases BMD loss and may increase fracture risk 2-fold. Carbamazepine and valproate both possess antiandrogen effects. Additionally, all anticonvulsants may indirectly inhibit osteoblast formation. The effects of anticonvulsants on BMD are dependent on duration of treatment.[6]

The 3 main bone cells (osteoblasts, osteocytes, and osteoclasts) contain functional serotonin receptors, which can alter bone metabolism.[6] It has been hypothesized that selective serotonin reuptake inhibitors (SSRIs) modulate the serotonin receptors located within bone, either directly and/or indirectly. Gut-derived serotonin appears to act on osteoblasts directly to decrease proliferation. Brain-derived serotonin appears to favor bone mass formation indirectly through inhibition. Further research is necessary to understand to what extent SSRIs impact bone health.[11]

As pharmacists engage in completing comprehensive medication therapy reviews, as part of the medication therapy management process, they can identify patients taking medication(s) associated with an increased risk of osteoporosis. During the patient encounter, pharmacists can engage in conversation to discuss the risks and benefits of continued use of medication(s) related to bone health and create a patient-specific medication action plan to address the identified medication-related problem(s). Following discussion with the patient, pharmacists may work with the patient's medical provider to suggest modification of therapy.

Screening recommendations

Osteoporosis is often regarded as being a problem for elderly Caucasian women. This commonplace notion, al-

TABLE 2

OVERVIEW OF GUIDELINE RECOMMENDATIONS FOR OSTEOPOROSIS SCREENING AND INITIATION OF TREATMENT

Guideline	BMD screening	Initiation of treatment
National Osteoporosis Foundation (NOF)	· Women age ≥65 yrs, men age ≥70 yrs · Postmenopausal women & men between age 50 and 69 yrs at risk for fracture(s) · All patients age ≥50 yrs with previous fracture(s)	· All patients with hip or spine fracture (symptomatic or asymptomatic) · Patients with T-score ≤-2.5 at femoral neck, total hip, or lumbar spine · Postmenopausal women & men age ≥50 yrs with osteopenia at femoral neck, total hip, or lumbar spine and 10-year hip fracture probability ≥3% or 10-year major osteoporotic-related fracture probability ≥20%
U.S. Preventive Services Task Force (USPSTF)	· Women age ≥65 yrs · Women age <65 yrs with fracture risk greater than or equal to that of a 65-year-old Caucasian woman with no additional risk factors · Current evidence insufficient to assess balance of benefits and harms of screening for osteoporosis in men	No specific recommendations for initiation of treatment
American College of Obstetricians and Gynecologists (ACOG)	· All postmenopausal women age ≥65 yrs · Postmenopausal women age <65 yrs with at least 1 osteoporosis risk factor · All postmenopausal women with previous fracture(s)	· Postmenopausal women who have experienced a fragility or low-impact fracture · Postmenopausal women with T-score <-2.0 in the absence of risk factors · Women with T-score <-1.5 in presence of 1 or more risk factors
North American Menopause Society (NAMS)	· All women age >65 yrs, regardless of clinical risk factors · Postmenopausal women with medical causes of bone loss (steroid use or hyperparathyroidism), regardless of age · Postmenopausal women age >50 yrs, with additional risk factors	· All postmenopausal women with osteoporotic vertebral or hip fracture · All postmenopausal women with T-score ≤-2.5 at lumbar spine, femoral neck, or total hip region · All postmenopausal women with T-score between -1.0 and -2.5 and FRAX major osteoporotic fracture probability ≥20% or hip fracture probability ≥3%
American Association of Clinical Endocrinologists (AACE)	· All women age ≥65 yrs · Younger postmenopausal women at increased fracture risk	· Patients with history of hip or spine fracture(s) · Patients with T-score ≤-2.5 regardless of history of fracture(s) · Patients with T-score between -1.0 and -2.5 and FRAX major osteoporotic fracture probability ≥20% or hip fracture probability ≥3%
The Endocrine Society	· All men age ≥70 yrs · Men age 50–69 yrs with additional risk factors	· Men with previous hip or vertebral fracture(s) · Men with T-score ≤-2.5 · Men with T-score between -1.0 and -2.5 and FRAX major osteoporotic fracture probability ≥20% or hip fracture probability ≥3% · Men receiving long-term glucocorticoid therapy (prednisone or equivalent >7.5 mg/d)

Abbreviations: BMD, bone mineral density; FRAX, Fracture Risk Assessment

Source: Ref 1,5,14–17

though correct, has the potential to delay both prevention and treatment in all men and women.[4] Pharmacists can fill this void by identifying individuals with multiple osteoporosis-related risk factors and suggesting and/or completing, when possible, BMD testing using dual-energy x-ray absorptiometry (DXA). The purpose of a DXA scan is to measure BMD at the femoral neck, total hip, and/or lumbar spine. The use of a DXA scan is beneficial in assessing bone health as well as in predicting an individual's future fracture risk. Ultimately, the DXA scan results confirm a diagnosis of osteopenia and/or osteoporosis.

The results of a DXA scan are expressed as grams per square centimeter (g/cm^2) and are commonly referred to as a T-score or Z-score. An individual's T-score represents a comparison between the optimal or peak BMD of a healthy 30-year-old adult and his or her own BMD. As an individual's BMD differs from that

of the standard norm, it decreases in standard deviation (SD) units; therefore, the lower the T-score (negative SD), the higher the risk of fracture. The Z-score simply represents a comparison of BMD with that of another individual of similar age. Z-scores are useful in the clinical setting as well, during diagnosis of secondary osteoporosis, to identify younger individuals who have not achieved peak bone mass. The most common cause of secondary osteoporosis is long-term use of glucocorticoids. Because BMD decreases with age, the Z-score can be misleading among older adults.[12] Therefore, it is an individual's T-score that determines a diagnosis of osteoporosis.

The World Health Organization (WHO) classifies BMD based on T-score. Per the WHO, a normal BMD is defined as a T-score of ≥-1.0. Oteopenia is defined as a T-score between -1.0 and -2.5; whereas osteoporosis is defined as a T-score of ≤-2.5. Severe or established osteoporosis is defined as a T-score of ≤-2.5 with ≥1 fracture.[13]

Several organizations publish clinical practice recommendations for osteoporosis regarding the appropriate time to start screening and initiating pharmacotherapy (**Table 2**, page 46).[1,5,14-17] The guidelines also include recommendations on daily consumption of calcium and vitamin D. The majority of organizations that publish clinical guidelines that address calcium and vitamin D supplementation support the recommendations of the NOF.

The NOF guidelines are widely used for osteoporosis management and are referenced by other clinical practice guidelines. Per the NOF, the 2 osteoporosis screening options are bone densitometry technology and vertebral imaging. The "gold standard" in osteoporosis screening is the DXA scan. Additional bone densitometry technologies are not as commonly used as DXA, but include quantitative computed tomography (QCT), peripheral QTC (pQTC), peripheral dual-energy x-ray absorptiometry (pDXA), and quantitative ultrasound densitometry (QUS).[1]

The NOF recommends considering BMD testing in the following populations: women age 65 and older, younger postmenopausal women, women in the menopausal transition, men age 70 and older, and men between the ages of 50 and 69 years (after assessing fracture risk). Any adult, regardless of gender, should have BMD testing performed if he/she experiences a fracture after the age of 50, has a condition associated with or increasing the risk of a fracture, or takes a medication associated with low bone mass or bone loss, as described above.[1]

An individual's T-score represents a comparison between the optimal or peak BMD of a healthy 30-year-old adult to his or her own BMD.

Following screening, there is an indication for particular at-risk populations to receive pharmacological treatment and/or calcium and vitamin D supplementation to prevent further decline in bone health and subsequent fractures. All patients with a hip or spine fracture, whether symptomatic or asymptomatic, and patients with a T-score of ≤-2.5 at the femoral neck, total hip, or lumbar spine should receive pharmacological treatment. In addition, postmenopausal women and men 50 years of age or older with osteopenia at the femoral neck, total hip, or lumbar spine as well as a 10-year hip fracture probability of ≥3% or a 10-year major osteoporotic-related fracture (clinical spine, forearm, hip, or shoulder) probability of ≥20% should receive pharmacological treatment.[1,18] Pharmacological treatment for osteoporosis will be described in detail in next month's continuing education program.

WHO developed the Fracture Risk Assessment (FRAX) tool supported by a broad international collaboration and validated in 2 large US cohorts.[14,18] The FRAX, available online (*http://www.shef.ac.uk/FRAX/*) at no cost, assesses the 10-year probability of a major osteoporotic-related fracture and 10-year probability of a hip fracture. This tool takes into account a number of patient-specific factors, including age, sex, lifestyle (smoking status and alcohol use), weight, height, medication use, and parental fracture history in determining risk. Of note, the FRAX tool is country- and race-specific; guidance is provided to assist in question response. Although the FRAX is considered most effective when a previous BMD result at the femoral neck is provided, inclusion of a BMD result is not required to estimate fracture risk. Results of the FRAX are used to identify persons who are likely to benefit from BMD testing and to guide treatment decisions; it is not used as a diagnostic measure.[18]

After initiating treatment, the NOF recommends BMD testing within 1 to 2 years and then every 2 years thereafter. If no diagnosis of osteoporosis is made, the NOF supports the U.S. Preventive Services Task Force (USPSTF) recommendation in which all women 65 years of age or older, and younger women whose fracture risk is equal to or greater than that of a 65-year-old Caucasian woman with no additional risk factors, undergo BMD testing.[1,14] For the latter, the corresponding 10-year probability of a major osteoporotic fracture, known as a FRAX score, is 9.3% or greater. The USPSTF concludes that current evidence is insufficient to assess the balance of benefits and

Pause&Ponder

Given your workflow, how might you identify and talk with patients who are taking medications that may increase their risk for osteoporosis?

harms of screening for osteoporosis in men. Additionally, BMD testing is not appropriate in children or adolescents, and healthy young men or premenopausal women should not routinely complete BMD testing unless there are specific risk factors for bone loss.[14] The USPSTF does not provide recommendations regarding initiation of treatment.

The American College of Obstetricians and Gynecologists (ACOG) has published clinical practice recommendations that are similar to the NOF guidelines; however, the primary focus is on women's health. Like the NOF, ACOG suggests BMD testing for all postmenopausal women 65 years of age or older or with a previous fracture (or fractures). However, ACOG specifies that postmenopausal women younger than 65 years of age who have at least 1 risk factor for osteoporosis undergo BMD screening. In the absence of a formal osteoporosis diagnosis, ACOG recommends performing BMD testing no more than every 2 years in women who do not have osteoporosis-related risk factors. Per ACOG, initiation of treatment is determined based on a woman's T-score. Postmenopausal women who have experienced a fragility or low-impact fracture, a T-score of <-2.0 in the absence of risk factors, or a T-score <-1.5 in the presence of 1 or more risk factors should receive treatment for osteoporosis.[15]

Like the NOF, the North American Menopause Society (NAMS) supports BMD testing in all women age 65 and older regardless of clinical risk factors. Furthermore, NAMS recommends that postmenopausal women with medical causes of bone loss (steroid use, hyperparathyroidism) regardless of age, and postmenopausal women age 50 and older with additional risk factors, undergo BMD screening. NAMS recommends that all postmenopausal women who have had an osteoporotic vertebral or hip fracture and all postmenopausal women with BMD values consistent with osteoporosis (T-score <-2.5) at the lumbar spine, femoral neck, or total hip region receive treatment. NAMS also recommends treatment in postmenopausal women with a T-score between -1.0 and -2.5 and a 10-year probability (FRAX score) of major osteoporotic fracture of at least 20% or a 10-year probability (FRAX score) of hip fracture of at least 3%.[5]

Similarly to other organizations, the American Association of Clinical Endocrinologists (AACE) recommends screening for osteoporosis in all women 65 years of age or older. In addition, younger postmenopausal women, despite age, who are at an increased fracture risk should undergo BMD screening. Pharmacologic treatment per AACE is indicated for patients with a history of a fracture at either the hip or spine and in those with a T-score of ≤-2.5 regardless of a history of fracture. Patients with a T-score between -1.0 and -2.5 and a FRAX major osteoporotic fracture probability of ≥20% or hip fracture probability of ≥3% should also receive treatment.[16]

The Endocrine Society publishes clinical guidelines specifically for the screening and treatment of osteoporosis in men. Like the NOF, the Endocrine Society recommends screening for osteoporosis in all men who are 70 years of age or older. The Endocrine Society also specifies that men between the ages of 50 and 69 years with additional risk factors, such as fracture prior to the age of 50, hypogonadism, or hyperthyroidism, should undergo BMD testing via DXA scan. It is stated that men who have experienced a previous hip or vertebral fracture, have a T-score of ≤-2.5, or are receiving long-term glucocorticoid therapy (prednisone or equivalent of >7.5 mg/d) should receive osteoporosis treatment. Men with osteopenia (T-score between -1.0 and -2.5) as well as those with a 10-year hip fracture probability of ≥3% or a 10-year major osteoporotic fracture probability of ≥20% are also candidates for pharmacologic treatment.[17]

Calcium and vitamin D

In conjunction with appropriate screening and initiation of pharmacologic treatment, many guidelines support adequate intake of calcium and vitamin D, either through dietary sources (preferred) or supplementation, to promote bone health. The NOF recommends that women 50 years of age or older and men older than 70 years of age target a daily calcium consumption of 1,200 mg. Men up to age 70 need only target 1,000 mg of calcium per day. All individuals 50 years of age or older, regardless of gender, should target 800 to 1,000 international units (IU) of vitamin D per day.[1] All organizations that publish clinical practice recommendations for osteoporosis screening either recommend the same amount of daily calcium and vitamin D intake or simply state support for the NOF recommendations.[5,15-17, 19]

Recent evidence has surfaced regarding cardiovascular (CV) risks of calcium and vitamin D supplementation. A number of studies are published on this topic, but only a select few are discussed herein. Details of these trials are outlined in **Table 4** (page 49).[20-24]

Discussion started in 2008, when a secondary analysis of a calcium supplementation study suggested that there

TABLE 3

FOODS RICH IN CALCIUM AND VITAMIN D

Calcium	
Food (quantity)	**Amount (mg)**
Fortified oatmeal (1 packet)	350
Sardines (3 oz can)	324
Cheddar cheese (1½ oz shredded)	306
Nonfat milk (1 cup)	302
Low-fat plain yogurt (1 cup)	300
Baked beans (1 cup)	142
Vitamin D	
Food (quantity)	**Amount (IU)**
Salmon (4 oz)	1059
Sardines (3.20 oz)	175
Goat's milk (1 cup)	124
Eggs (1 each)	26
Shiitake mushrooms (87 g)	17

Abbreviation: IU, international units

Source: Ref 26

TABLE 4

SUMMARY OF SELECT TRIALS INVOLVING CALCIUM AND VITAMIN D SUPPLEMENTATION

Trial	Inclusion criteria	Exclusion criteria	Intervention	Primary outcomes	Results
Bolland et al, 2008 Secondary analysis of randomized, placebo-controlled study in New Zealand Patients followed every 6 mo for 5 yrs	• Women age ≥55 yrs • Postmenopausal for at least 5 yrs • Life expectancy >5 yrs	• Treated for osteoporosis • Taking calcium supplements • Major ongoing disease (renal, bone, hepatic, malignancy, thyroid dysfunction) • Vitamin D deficiency (25-hydroxyvitamin D levels <10 ng/mL)	• Calcium citrate supplementation 400 mg before breakfast and 600 mg in evening (n=732) • Placebo (n=739)	Adverse CV events (death, sudden death, MI, angina, other chest pain, stroke, TIA) and composite end point (MI, stroke, or sudden death)	• 36 events in intervention group vs 22 in control group had MI (RR 1.49; 95% CI 0.86–2.57, *P*=0.16) • 37 events in intervention group vs 26 in control group had stroke (RR 1.37; 95% CI 0.83–2.28, *P*=0.23) • 76 events in intervention group vs 54 in control group with composite end point (RR 1.21; 95% CI 0.84–1.74, *P*=0.32)
Bolland et al, 2010 Meta-analysis of double-blind, placebo-controlled trials; CV data available as patient level and trial level data	• 100 patients • Mean age ≥40 yrs • Trial more than 1 year in duration • Taking ≥500 mg/d of calcium supplements	• Vitamin D supplementation given only to the intervention group • Majority of patients had major systemic disease (other than osteoporosis) • Calcium administered in form of dietary modification	Calcium supplementation ≥500 mg/d	• MI • Stroke • First event (composite of MI, stroke, or sudden death)	**Patient level** (5 trials; n=8151; mean follow-up 4 yrs): • 143 in intervention group vs 111 in control group had MI (HR 1.31; 95% CI 1.02–1.67, *P*=0.035) • 167 in intervention group vs 143 in control group had a stroke (HR 1.20; 95% CI 0.96–1.50, *P*=0.11) • 293 in intervention group vs 254 in control group had an event (HR 1.81; 95% CI 1.00–1.39, *P*=0.057) **Trial level** (8 trials; median follow-up 3.6 yr): • 166 in intervention group vs 130 in control group had MI (RR 1.27; 95% CI 1.01–1.59, *P*=0.038)
Bolland et al, 2011 Updated prior meta-analysis with data from WHI CaD Study					**Patient level** (6 trials, n=24,869): • 631 in intervention group had MI (HR 1.26; 95% CI 1.07–1.47, *P*=0.005) • 669 in intervention group had stroke (HR 1.19; 95% CI 1.02–1.39, *P*=0.03) **Trial level** (9 trials): • 676 in intervention group had MI (RR 1.24; (95% CI 1.07–1.45, *P*=0.004)
Li et al, 2012 n=25,540 Mean follow-up 11 years	• Age 35–64 yrs • Free of major CVD events at recruitment	• Previous MI, TIA, or stroke • Extremely low or high caloric intake	Assessed impact of calcium as a calcium supplement, calcium as part of a multivitamin, or calcium through dietary intake	Incidence of CV event (MI, stroke, CVD mortality)	Adjusted results: • Calcium supplementation increased risk of MI compared to risk for nonusers of supplements (HR 1.86; 95% CI 1.17–2.96) • Calcium supplementation did not increase risk of stroke (HR 1.05; 95% CI 0.55–1.99) or overall CVD mortality (HR 1.02; 95% CI 0.51–2.00)
Wang et al, 2010 Systematic review	• Prospective studies or randomized controlled trials in English • Search terms: vitamin D supplements, calcium supplements, CVD events	Cross-sectional, retrospective case-control, ecologic, case reports, studies of children and adolescents	Vitamin D supplementation, calcium supplementation, or both	Reduction of risk for CV events	9 prospective studies and 8 randomized controlled trials: • Pooled RR of CVD 1.14 (95% CI, 0.92–1.41) for calcium supplements vs placebo • Pooled RR of CVD 1.04 (95% CI, 0.92–1.18) for combined vitamin D plus calcium supplements

Abbreviations: CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; HR, hazard ratio; MI, myocardial infarction; RR, relative risk; TIA, transient ischemic attack; WHI CaD, Women's Health Initiative Calcium/Vitamin D Supplementation Study

Source: Ref 20–24

may be an increased risk of CV events in older women taking calcium supplementation for at least 5 years; however, limitations exist. Of note, originally this study was designed to examine the effects of calcium supplementation on fracture risk and BMD. It represented a small population, mainly older Caucasian women, and had a high drop-out rate (336 women in the calcium group and 296 women in the placebo group) prior to the 5-year end point. Furthermore, there may have been variability in cardiac risk factors, such as use of hormone supplementation, that was not accounted for between groups.[20]

Several years later, in 2010, a meta-analysis suggested the potential of calcium supplementation to increase the risk of myocardial infarction (MI). There was a positive association between calcium supplementation and MI risk in both patient level and trial level data. No association was found between calcium supplementation and stroke risk or occurrence of a CV event (composite of MI, stroke, or sudden death). In this analysis, the average daily dose of calcium supplementation was 1,000 mg and most study participants were women. Noteworthy limitations are that the incorporated trials did not have CV outcomes as primary end points and the researchers counted CV events rather than the number of people with CV events. They concluded that calcium supplementation of more than 500 mg per day, without vitamin D supplementation, is associated with about a 30% increased risk of MI.[21]

This meta-analysis was later updated and included the data of women not taking calcium at randomization who participated in the Women's Health Initiative Calcium/Vitamin D Supplementation Study. In the reanalysis of patient data, findings suggested that the number needed to treat with calcium with or without vitamin D for 5 years to cause 1 MI was 240, whereas the number needed to treat to prevent 1 fracture was 302. This difference suggests a greater risk than benefit of calcium with or without vitamin D supplementation.[22]

The pharmacist is not only in a position to recognize when to recommend screening and initiation of treatment per specified guidelines, but is also able to determine appropriate candidates for self-care.

A large prospective German cohort study assessed the association between calcium intake and MI, stroke, and CV mortality. Results were adjusted for sex, age at enrollment, education, activity, BMI, smoking, alcohol use, calorie-adjusted dietary calcium intake, vitamin D intake, saturated fat, protein, and caloric intake, hyperlipidemia, diabetes, and nonsteroidal anti-inflammatory drug use. Findings of the study suggested that use of calcium supplementation, as calcium solely or as part of a multivitamin, increased MI risk. Patient recall of dietary and calcium intake and no report of daily calcium supplementation were limitations of this study.[23]

In a recent systematic review on vitamin D and calcium supplementation in the prevention of CV events, 4 randomized trials focused on calcium supplementation. Although there was an increase in reported CV events, there was no statistical significance. Furthermore, prospective and randomized trials showed no effect on calcium supplementation, with or without vitamin D, on the risk for CV events.[24]

Pause&Ponder

How might you respond to a patient inquiring about calcium and vitamin D supplementation and the risk for cardiovascular events?

Given the variability of results and limitations of the studies regarding the impact of calcium supplementation, with or without vitamin D, on CV events, pharmacists should recommend calcium and vitamin D intake through dietary sources. It is useful to recommend consumption of dietary calcium through calcium-rich foods, such as yogurt or cheese, or calcium-fortified products, such as orange juice, before advising use of supplements to meet the recommended daily allowances (RDA) outlined in **Table 1** (page 44).[4-6] Consumption of vitamin D through natural food sources, such as salmon or egg yolk, or vitamin D-fortified foods, such as milk or cereal, is advisable to reach RDA.[4]

Despite the availability of consistent evidence regarding adverse outcomes with calcium, with or without vitamin D supplementation, the USPSTF states that current evidence is insufficient to assess the benefits and risks of combined vitamin D and calcium supplementation for the primary prevention of fractures in premenopausal women or in men. USPSTF also states that current evidence is insufficient to assess the benefits and risks of daily supplementation with >400 IU of vitamin D and >1,000 mg of calcium for the primary prevention of fractures in noninstitutionalized postmenopausal women. Furthermore, the USPSTF recommends against daily supplementation with 400 IU or less of vitamin D and 1,000 mg or less of calcium for the primary prevention of fractures in noninstitutionalized postmenopausal women.[25]

Patient self-care

The pharmacist is not only in a position to recognize when to recommend screening and initiation of treatment per

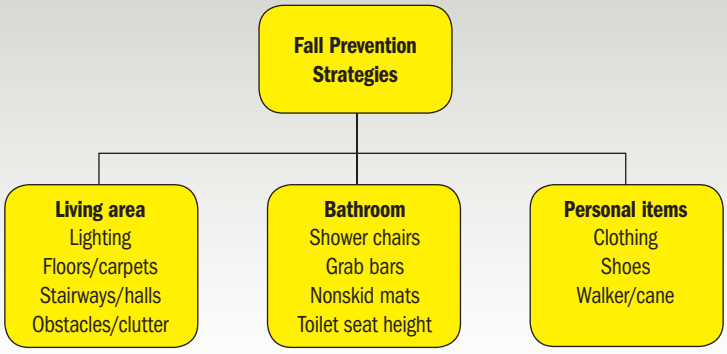
specified guidelines but is also able to determine appropriate candidates for self-care. Pharmacists can recommend self-care options to patients through lifestyle modifications, such as physical activity, dietary changes, and smoking cessation. Patients should be encouraged to participate in weight-bearing exercises, including walking, jogging, or dancing as well as strength-training exercises with small dumbbells and resistance bands. Additional activities that can improve range of motion and overall bone health include light stretching and performing tasks to strengthen balance. Dietary changes that benefit patients with osteoporosis are consumption of foods rich in calcium and vitamin D. **Table 3** (page 48) provides some common dietary sources of calcium and vitamin D.[26]

All current smokers should be encouraged to engage in smoking cessation. Tools available to the pharmacist to assess a patient's dependence on nicotine and readiness and motivation to quit include the Fagerström Test for Nicotine Dependence (FTND) and 5As and 5Rs, respectively. The 5As include asking the patient about his or her current smoking status, advising to quit, assessing willingness to quit, assisting in a quit attempt, and arranging follow-up. The 5Rs are relevance, risks, rewards, roadblocks, and repetition, all of which target the patient's motivators and barriers to quitting. It is important for the pharmacist to assist patients in product selection based on the number of cigarettes smoked per day or the amount of time before the first cigarette of the day. Pharmacists should also provide counseling to patients on appropriate use of smoking cessation products as well as potential side effects of therapy.[27]

Furthermore, pharmacists can educate older adults on fall prevention strategies (**Figure 1**).[5,28] Within the living area, patients should be advised to install adequate lighting and handrails to facilitate safe passing around the home. All potential obstacles and hazards such as coffee tables, slippery rugs, and loose wires should be removed. Furniture, including couches and chairs, should be arranged in a fashion that allows for clear pathways. Installation of grab bars in the tub or shower, and near the toilet is an ideal fall prevention strategy. Individuals should be encouraged to wear comfortable shoes with tied laces and thick soles; clothing should also be fitted and free of any hanging fabrics and restrictive accessories. In addition to recommending environmental modifications, pharmacists should review and assess a patient's medication list, as some medications, including tricyclic antidepressants and opioids, may increase the risk of falls. Drug-related risk factors should be evaluated and should include dose, time since initiating medication, and number of medications. By performing a comprehensive medication review, pharmacists can assist in eliminating any unnecessary or duplicate therapies, recommend dose modifications, suggest appropriate titration schedules, and implement monitoring parameters.[5,28]

FIGURE 1

FALL PREVENTION STRATEGIES FOR THE HOME



Source: Ref 5, 28

Conclusion

As the prevalence of osteoporosis rises, pharmacists can intervene in a variety of ways, all of which align with the core components of medication therapy management. Patients will appreciate discussions about risk factors and potential modifications that reduce their risk for developing osteoporosis. In addition, pharmacists can identify patients at risk for a future fracture, not only on the basis of medication use, but also through determination of a FRAX score. Once identified, patients should be encouraged to complete BMD testing and to receive treatment based on the results. Regardless of results, older adults should be counseled on ways to reduce fall risk. Pharmacists also need to stay abreast of various guideline recommendations for osteoporosis screening and treatment; in doing so, pharmacists can educate patients and follow the recommendations.

Although intake of calcium and vitamin D is important for strengthening bones, data on calcium and vitamin D supplementation and cardiovascular risk are inconclusive. Further studies are needed to determine the etiology of this association and its risk. Pharmacists should be familiar with dietary sources of calcium and vitamin D, so that they can assess intake through food consumption and recommend supplementation if necessary.

References posted online at:
www.drugtopics.com/cpe

For immediate CPE credit, take the test now online at:

www.drugtopics.com/cpe
Once there, click on the link below "Free CPE Activities."

TEST QUESTIONS

1. There are 3 primary cells responsible for bone modeling and remodeling. Identify which of the following is correctly matched to its physiologic role in homeostasis:

a. Osteoclasts build the collagen matrix
b. Osteocytes break down the collagen matrix
c. Osteoblasts break down the collagen matrix
d. Osteoclasts break down the collagen matrix

2. Parathyroid hormone (PTH) is considered 1 of 4 main metabolic regulators for bone health. What is the role of PTH in bone homeostasis?

a. Prevents bone breakdown by inhibiting osteoclasts
b. Enhances calcium absorption in the gastrointestinal tract
c. Stimulates calcitriol production and conservation of calcium by the kidneys
d. Modulates the RANKL-RANK pathway

3. Which of the following statements correctly describes estrogen's impact on osteoblast formation?

a. Stimulates proliferation and decreases apoptosis
b. Stimulates proliferation and increases apoptosis
c. Decreases proliferation and decreases apoptosis
d. Decreases proliferation and increases apoptosis

4. Approximately how many people suffer an osteoporotic-related fracture annually?

a. 1 million **b.** 1.5 million
c. 2 million **d.** 2.5 million

5. Approximately how many people older than age 50 years currently have a diagnosis of osteoporosis?

a. 8 million **b.** 10 million
c. 12 million **d.** 15 million

6. Which of the following is considered a risk factor for osteoporosis?

a. Age <50 years
b. Male sex
c. Sedentary lifestyle
d. No history of fractures

7. Which of the following is the recommended time for physical activity in a relatively inactive individual beginning an exercise regimen?

a. 20–30 min/d
b. 5–10 min/d
c. 10–15 min/d
d. Individuals should consult with their physician prior to beginning any physical activity.

8. DS is a 77-year-old male who takes metformin, lisinopril, omeprazole, and pravastatin. Which of these medications may place him at an increased risk for osteoporosis?

a. Pravastatin **b.** Omeprazole
c. Lisinopril **d.** Metformin

9. In which of the following areas does a dual-energy x-ray absorptiometry (DXA) scan measure bone mineral density (BMD)?

a. Lumbar spine **b.** Femoral neck
c. Total hip **d.** All of the above

10. SK, a 75-year-old female, is told by her primary care provider that the result of her DXA scan reveals osteopenia. Which of the following T-scores is classified as osteopenia?

a. T-score ≤-2.0
b. T-score ≤-1.5
c. T-score between -1.0 and -2.5
d. T-score ≥-1.0

11. Which of the following guidelines does not provide a recommendation for the initiation of osteoporosis treatment?

a. American Association of Clinical Endocrinologists (AACE)
b. American College of Obstetricians and Gynecologists (ACOG)
c. U.S. Preventive Services Task Force (USPSTF)
d. North American Menopause Society (NAMS)

12. The National Osteoporosis Foundation (NOF), ACOG, AACE, and NAMS guidelines recommend initiation of treatment for osteoporosis primarily based on which of the following:

a. Z-score
b. T-score
c. FRAX probability
d. Number of risk factors

13. A 58-year-old woman's DXA scan reveals T-scores of -1.6 and -2.3 at the lumbar spine and hip, respectively. Her FRAX indicates a 4.1% 10-year probability of a hip fracture and a 16% 10-year probability of a major osteoporotic fracture. Using the AACE guidelines, which of the following statements is true?

a. She is not a candidate for osteoporosis treatment.
b. She is a candidate for osteoporosis treatment based on her T-scores alone.
c. She is a candidate for osteoporosis treatment based on her T-score at the lumbar spine and 10-year probability of a major osteoporotic fracture.
d. She is a candidate for osteoporosis treatment based on her T-score at the hip and her 10-year probability of a hip fracture.

14. LM is a 68-year-old Caucasian female who currently smokes and has a body mass index of 17 kg/m^2. Her last DXA scan revealed a T-score of -1.8. Based on current ACOG guidelines, LM is a candidate for which of the following?

a. Calcium intake of 1200 mg/d
b. Osteoporosis treatment
c. Vitamin D intake of 1,000 IU/d
d. All of the above

15. Which of the following statements is true regarding the meta-analysis published in 2010 by Bolland et al?

a. In the patient level data, there was a statistically significant increase in stroke with calcium supplementation.
b. In the trial level data, there was a statistically significant increase in myocardial infarction (MI) with calcium supplementation.
c. In the trial level data, there was a statistically significant increase in stroke with calcium supplementation.
d. In the trial level data, there was a statistically significant increase in the composite of MI, stroke, or sudden death with calcium supplementation.

16. AK, a 54-year-old female, comes to your pharmacy to inquire about calcium and vitamin D supplementation. Based on available evidence surrounding supplement use, which of the following is the best response?

a. "You should never use calcium and vitamin D supplements. You'll have a heart attack!"
b. "You definitely need calcium and vitamin D supplementation! I recommend 1,200 mg calcium and 800 IU vitamin D daily."
c. "You don't really need calcium and vitamin D supplements. There are no recommended daily allowances."
d. "You may need calcium and vitamin D supplementation. Tell me first about how much calcium and vitamin D you consume daily in your diet."

17. The NOF recommends daily consumption of 1200 mg of calcium in which of the following individuals:

a. All adults ≥50 years of age
b. Women ≥65 years only
c. Women ≥65 years and men ≥75 years
d. Women ≥50 years and men ≥70 years

18. Which of the following foods has the highest amount (in IU) of vitamin D?

a. Salmon **b.** Eggs
c. Shiitake mushrooms **d.** Sardines

19. Which of the following ways can a pharmacist impact patient self-care in prevention of osteoporosis?

a. Encourage smoking cessation
b. Encourage weight-bearing exercises
c. Recommend BMD testing
d. All of the above

20. RZ is a 56-year-old female who had a fracture at the age of 51. Based on current NOF guidelines, RZ is a candidate for which of the following?

a. DXA scan
b. Daily calcium intake of 100 mg/d
c. Daily vitamin D intake of 1,000 IU/d
d. a and c

LEGAL COMPLIANCE Ned Milenkovich, PharmD, JD

Compounding pharmacies bring health plan lawsuit

Insurer wrongly excluded coverage of compounded drugs, they charge

Three compounding pharmacies have sued Harvard Pilgrim Health Care (Harvard Pilgrim) in Massachusetts. The lawsuit, filed in Norfolk Superior Court, alleges that Harvard Pilgrim violated state law as well as its contractual obligations by denying health insurance coverage for drug preparations compounded by the pharmacies. Harvard Pilgrim is the second largest insurer in the state of Massachusetts.

The plaintiff pharmacies involved in the lawsuit are Bird's Hill Pharmacy, Hopkinton Drug, and Johnson Compounding and Wellness Center. In addition to seeking an injunction to halt the coverage exclusion, the plaintiffs sought a trial by jury and damages related to lost business.

The back story

In short, in July 2013 the plaintiffs filed the lawsuit and sought a preliminary injunction to prevent Harvard Pilgrim from denying medically necessary healthcare services. Harvard Pilgrim had introduced a change in its prescription-drug policy through a policy shift in prescription-drug benefits scheduled to take effect in August 2013.

A separate federal lawsuit was filed by a Harvard Pilgrim insured individual in U.S. District Court in Boston, Massachusetts.

Bird's Hill Pharmacy owner, Henry Abbott, was quoted in a statement as saying, "Harvard Pilgrim's callous decision to cut off coverage is a major blow to the many patients across Massachusetts who depend on compounded medications, either because there is no commercially manufactured drug available or because they need a customized version. Many of our patients will no longer be able to afford these medications without insurance coverage, and we are worried about what this decision will mean for their health."

Adults only

Of interest, the Harvard Pilgrim policy shift excludes coverage only for prescription drugs compounded for adults, while continuing coverage for children. Specifically, the policy change will affect only Harvard Pilgrim members over age 18; however, an appeals process is available to those adults who wish to attempt to request coverage for a compounded prescription drug once coverage is denied.

Compounded drugs are prepared by pharmacies pursuant to patient-specific prescriptions for individuals who are unable to obtain commercially available preparations or who may have allergies to one or more components of a standard drug.

Federal and state regulators, as well as payors, have increased their scrutiny of compounding pharmacies recently due to injuries and deaths arising from unsafe practices related to the preparation of compounded prescription drugs.

The argument

The substantive aspect of the legal complaint argues that Harvard Pilgrim is statutorily mandated to provide coverage for "healthcare services that are ordered by a treating physician or a primary care provider if (1) the services are a covered benefit under the insured's health benefit plan and (2) the services are medically necessary."

The plaintiff pharmacies claim that in many instances standard medications are not commercially available for certain conditions. They maintain that because some patients cannot be prescribed standard medications because they are allergic or have other health conditions, compounded prescription drugs are medically necessary.

In response to the lawsuit, Harvard Pilgrim issued the following statement: "We are in the process of carefully reviewing the plaintiffs' allegations with our legal counsel. However, we do want to emphasize that we have an established process to approve medically necessary compounded prescriptions within a 48-hour turn-around, once all information is received." DT

This article is not intended as legal advice and should not be used as such. When legal questions arise, pharmacists should consult with attorneys familiar with the relevant drug and pharmacy laws.

Ned Milenkovich *is a member at McDonald Hopkins, LLC, and chairs its drug and pharmacy practice group. He is also vice-chairman of the Illinois State Board of Pharmacy. Contact Ned at 312-642-1480 or at nmilenkovich@mcdonaldhopkins.com.*

LifeGuard's RobiComb is able to detect and kill lice on contact by eliminating the lice and their eggs.

Babo Botanicals' Lice Repel Shampoo and Conditioning Spray offer safe, all-natural alternatives to harsh chemicals.

Vidal Sassoon Pro Series Boost & Lift Foaming Air Mousse helps control unruly hair and provides up to 24 hours of strong, flexible hold.

PHOTOS COURTESY OF LIFEGUARD / BABO BOTANICALS / VIDAL SASSOON

OTC

Healthy hair products take aim at head lice, damaged/unruly locks

CHRISTINE BLANK

In the realm of health and beauty care, nowhere is innovation more prevalent than in the over-the-counter (OTC) hair-care category. During the past year, manufacturers have launched a special comb to zap lice, styling sprays designed to handle heat-treated hair, and unique moisturizing shampoos and conditioners. Below are just a few of the new hair-care products that are being sold in drugstores across the United States.

Treatments for head lice

Head lice are a major concern of parents as children head back to school. In fact, recent studies report that 75% of lice found in North America have become resistant to the most common active ingredient in the leading lice shampoo. As a result, LiceGuard recently introduced the **RobiComb**, which can be used regularly to detect and prevent future outbreaks. This innovative comb uses an audible signal to indicate the presence of new lice. Used on dry hair, the electronic comb detects and kills lice on contact, eliminating both the lice and their eggs.

At the same time, the technology behind shampoos for head lice is also evolving. Babo Botanicals' new **Rosemary Tea Tree Lice Repel Shampoo** and **Conditioning Spray** both feature a unique blend of rosemary, mint, and tea tree oil to provide a safe, all-natural alternative to harsh chemicals. The pesticide-free formulas repel lice while cleansing and conditioning hair with pure botanical ingredients. Both products are sold in 8-ounce bottles.

Styling products

There are many creative new products in the styling and hair protection category. **Vidal Sassoon Pro Series Boost & Lift Foaming Air Mousse** is one such advanced product. The mousse is formulated to allow a long working time for the desired style, so it helps control unruly hair. It provides up to 24 hours of strong, flexible hold and long-lasting volume.

"The Foaming Air Mousse was created after learning that consumers want touchable volume that will last and won't weigh hair down," a company statement said. The Boost & Lift Foaming Air Mousse does not feel sticky and combs out easily.

Meanwhile, **Beat the Heat Thermal Shield Spray** from Not Your Mother's protects hair from the heat of flatirons and curling irons. It guards hair against moisture loss and provides a light hold. The spray is infused with sunflower, vitamin A, and vitamin E. It is available in a 6-ounce container and in the 2-ounce travel size.

Beach lovers can consider Not Your Mother's **Beach Babe Texturizing Hair Cream**, which can be used to style hair after a day in the wind and waves.

Continued on pg. 56

GBS risk after influenza vaccination

Continued from pg. 39

typical reported rates. When investigators controlled for patients with a preceding gastrointestinal or respiratory illness, they noted only five cases of GBS in almost seven million influenza vaccine recipients. In 8.5 million doses of other vaccines administered to children, no reported cases of GBS followed.[5]

Perspective

This and other recent studies (e.g., Kwong, JC, et.al, 2013)[6] have cast a great deal of doubt on the possibility of a causal relationship between influenza vaccination and GBS. Furthermore, the increased risk of GBS following influenza infection lends additional support to use of influenza vaccination to reduce the likelihood of acquiring GBS via immunity to influenza.

Patients or providers concerned about GBS should keep this rare disease in perspective. Influenza infects up to 20% of the population and contributes to an average of 36,000 deaths annually, with highest rates of mortality in infants, the elderly, and individuals with chronic diseases.[1] With vaccine effectiveness for 2012-2013 estimated at 56%[7], it is clear that the reduction in influenza infection and death outweighs an unsupported one-in-a-million theoretical risk from vaccination. DT

References

1. Institute of Medicine. Immunization safety review: Influenza vaccines and neurological complications. Washington (DC): National Academy Press; 2004.
2. Tam CC, O'Brien SJ, Petersen I, et al. Guillain-Barré Syndrome and preceding infection with *Campylobacter*, influenza, and Epstein-Barr virus in the general practice research database. PLoS ONE 2007;2(4):e344. doi:10.1371/journal.pone.0000344.
3. Breman JG, Hayner NS. Guillain-Barré syndrome and its relationship to swine influenza vaccination in Michigan, 1976-1977. *Am J Epidemiol* 1984;119:880-9.
4. Institute of Medicine (U.S.). Adverse effects of vaccines: Evidence and causality. Washington (DC): National Academy Press; 2012.
5. Baxter R, Bakshi N, Fireman B, et al. Lack of association of Guillain-Barré syndrome with vaccinations. *Clin Infect Dis*. 2013; 57(2):197–204.
6. Kwong JC, Vasa PP, Campitelli MA, et al. Risk of Guillain-Barré syndrome after seasonal influenza vaccination and influenza health-care encounters: A self-controlled study. *Lancet Inf Dis*. 28 June 2013; DOI: 10.1016/S1473-3099(13)70104-X.
7. CDC. Interim adjusted estimates of influenza vaccine effectiveness — United States, February 2013. *MMWR*. 2013;62(7):119–23.

Mark Walberg *is assistant professor of pharmacy practice, University of the Pacific Thomas J. Long School of Pharmacy and Health Sciences, Stockton, Calif.*

Healthy hair products take aim at head lice

Continued from pg. 54

Not Your Mother's Beat the Heat Thermal Styling Shield Spray protects hair from the heat of flatirons and curling irons.

Not Your Mother's Beach Babe Texturizing Hair Cream can be used to style hair after a day in the wind and waves.

Not Your Mother's Lock Luster Oil Treatment helps to repair dry, damaged hair and protect it from heat and excessive styling.

Shampoos/conditioners

Shampoos and conditioners have also become more technologically advanced. Take **Dove Daily Moisture Shampoo and Conditioner.** The two products are based on a patented technology that goes down to the cellular level to moisturize hair. The Pro-Moisture Complex in the shampoo and conditioner are infused with a blend of essential amino acids that penetrate hair to help replenish lost proteins. They do not weigh the hair down with excess residue. The Dove Daily Moisture Shampoo and Conditioner are sold in 12-ounce bottles.

This year Dove also launched **Dove Intensive Repair Shampoo and Conditioner**, which contain ingredients it calls "Keratin Repair Actives." The shampoo and conditioner work on the keratin already present in hair to help repair damaged proteins, smoothing hair from root to tip and adding strength by reducing breakage. Featuring a new, improved fragrance, the Intensive Repair Shampoo and Conditioner also help to prevent split ends. Both products come in 12-ounce bottles.

Garnier Fructis Hydra Recharge Shampoo provides "a powerful new blast of hydration," with its encapsulated beads of superfruits goji berry, passion fruit, and kiwi. **Garnier Fructis Volume Extend Shampoo** uses papaya and cucumber extracts for long-lasting fullness.

Hair treatment

Recently, **Not Your Mother's** launched a new type of treatment designed to repair and nourish hair. Its **Lock Luster Oil Treatment**, which is infused with argan oil and macadamia oil, aids in repairing dry, damaged hair. The product also protects hair from heat and excessive styling, and detangles overworked hair. The product works well with all hair types, especially dry and damaged hair.

Garnier Fructis offers **Triple Nutrition Miracle Dry Oil spray** for hair, body, and face. The company has introduced its first multi-use spray, containing olive, avocado, and almond oils, to nourish dry hair and skin. The fortified fruit spray should be used 6 to 8 inches from hair and body, and should not be directly sprayed into the face. DT

Christine Blank, *a frequent contributor to* Drug Topics, *lives in Lake Mary, Fla.*

PHOTOS COURTESY OF NOT YOUR MOTHER'S

Advertiser Index

*Indicates a demographic advertisement.

RX & OTC

New flu vaccines for the 2013–2014 season and more

JULIA TALSMA, CONTENT CHANNEL DIRECTOR

RX CARE

New flu vaccines

The 2013-2014 influenza season is the first time that quadrivalent influenza vaccines will be available in the United States, protecting individuals against two strains of influenza A and two of influenza B. Previously, the only influenza vaccines available were trivalent, containing two strains of influenza A and one of influenza B.

At the end of July, MedImmune, the biologics arm of AstraZeneca, began shipping **FluMist Quadrivalent** [1] (Influenza Vaccine Live, Intranasal) Nasal-Spray Flu Vaccine to U.S. distributors for the 2013-2014 influenza season. Eligible patients are children two years and older and adults through 49 years of age. FluMist Quadrivalent Nasal-Spray Flu Vaccine will be available through private healthcare practices, public health departments, select retail pharmacies, school-located vaccination programs, military bases, and other sites. **(www.flumistquadrivalent.com)**

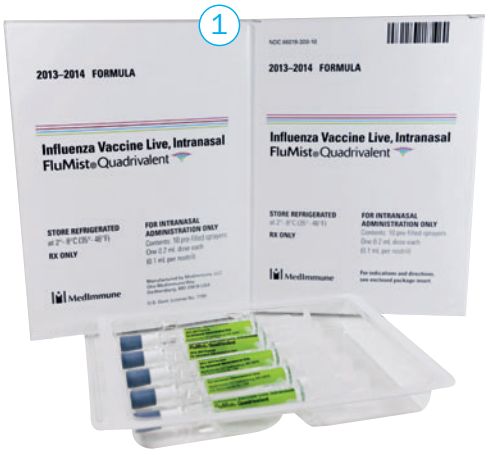
In July, GlaxoSmithKline (GSK) began shipping pre-filled syringes of its first quadrivalent vaccine, **Fluarix Quadrivalent**, for the 2013-2014 flu season. In August, FDA approved GSK's **FluLaval Quadrivalent** (Influenza Vaccine Virus) for adults and children 3 years of age and older to prevent A and B strains of seasonal flu. FluLaval Quadrivalent vaccine will be available only in the United States, in multi-dose vials, in limited amounts. Trivalent versions of both vaccines are also shipping. In 2014, GSK will have expanded capacity to supply the two vaccines, which will be manufacturered in Quebec, Canada (FluLaval Quadrivalent), and Dresden, Germany/Marietta, Pa. (Fluarix Quadrivalent). GSK is taking orders for FluLaval Quadrivalent at its website. (**http://gskvaccinesdirect.com**)

Sanofi Pasteur, the vaccine division of Sanofi, shipped the first lots

Continued on pg. 58

New flu vaccines for the 2013–2014 season and more

Continued from pg. 57



of its influenza virus vaccine for the 2013-2014 season at the end of July. Sanofi Pasteur is offering four **Fluzone** products: the Fluzone vaccine, the Fluzone quadrivalent vaccine, the Fluzone high-dose vaccine, and the Fluzone intradermal vaccine. **(www.sanofipasteur.us/vaccines)**

Novartis began shipping its influenza vaccines in mid-August. These include **Fluvirin**, approved for use by individuals four years of age and older, and **Flucelvax,** approved for use by adults who are at least 18 years of age. Flucelvax is the first FDA-approved influenza vaccine manufactured using cell-based technology. **(www.flucelvax.com)**

New drugs

In August, ViiV Healthcare, a GSK-associated company, announced FDA approval of **Tivicay** (dolutegravir) for the treatment of HIV-1 infection. This new integrase strand transfer inhibitor is formulated as a pill taken daily in combination with other antiretroviral drugs for HIV-infected individuals, either treatment-naïve or treatment-experienced, who may have been treated with other integrase strand transfer inhibitors. It is also approved for children who are 12 and older, who weigh at least 40 kg, and who have not been previously treated with other integrase strand transfer inhibitors. **(http://bit.ly/tivicay)**

Forest Laboratories has announced that **Fetzima [2]** (levomilnacipran extended-release capsules) was approved by FDA in July for the treatment of major depressive disorder in adults. Fetzima is a serotonin and norepinephrine reuptake inhibitor, to be taken once daily. It is available in 40-, 80-, and 120-mg strengths. **(www.fetzima.com)**

New indication

FDA has approved **Mirvaso**, the alpha-2 adrenergic agonist brimonidine from Galderma, to treat facial redness in adult patients with rosacea. According to a company statement, the new indication makes Mirvaso 0.33% topical gel the first topical treatment specifically indicated for the persistent facial erythema of rosacea. Applied once daily to the face, the gel remains effective for up to 12 hours. The drug is thought to constrict dilated facial blood vessels, which reduces the redness in rosacea. **(http://bit.ly/mirvaso)**

New formulations

Actavis has launched new formulations of **Fioricet** (butalbital, acetaminophen, and caffeine capsules, USP) and **Fioricet with Codeine** (butalbital, acetaminophen, caffeine, and codeine phosphate, USP) containing a lower dose of acetaminophen (reduced from 325 mg to 300 mg) designed to provide a safer treatment option for patients suffering from tension (or muscle contraction) headaches. The number of pills that may be prescribed, and the time interval at which they may be prescribed, will not change with the new formulations. **(www.actavis.com)**

New generics

Amneal is now shipping five new generic products to wholesalers and distributors. **Potassium chloride extended-release capsules** (therapeutically equivalent to Nesher's Micro-K10 ExtenCaps) are available in 750-mg strength in counts of 100, 500, and 1,000. **Sildenafil tablets** (therapeutically equivalent to Pfizer's Revatio) are available in 20-mg strength in a 90 count. **Nevirapine tablets, USP [3]** (therapeutically equivalent to Boehringer Ingelheim's Viramune), are available in 200-mg strength in a 60 count. **Metaxalone tablets** (therapeutically equivalent to King Pharmaceuticals' Skelaxin) are available in 800-mg strength in a 100 count. **Warfarin sodium tablets** (therapeutically equivalent to Bristol-Myers Squibb's Coumadin) are available in mg strengths of 1, 2, 2.5, 3, 4, 5, 6, 7.5, and 10 in a count of 100. **(www.amneal.com)**

Dr. Reddy's Laboratories has launched **divalproex sodium extended-release tablets, USP** (250 mg and 500 mg), a therapeutically equivalent generic version of Depakote ER Tablet. The 250-mg tablets are available in counts of 100; the 500-mg tablets in counts of 100 and 500. **(www.drreddys.com)** DT

PHOTOS COURTESY OF MEDIMMUNE / FOREST LABORATORIES / AMNEAL

NEW PRODUCT

"Finally, for the first time I can offer my customers PSE relief that's highly meth-resistant."

New Zephrex-D® helps patients and pharmacists breathe easier.

New Zephrex-D is the first and only cold and sinus medication that provides the unsurpassed decongestant performance of pseudoephedrine in a unique, patented formula that significantly disrupts illicit meth making*.

With Zephrex-D, you can offer a new standard of care that gives patients the relief they need while protecting their kids and communities from the dangers of meth.

WESTPORT PHARMACEUTICALS

*Conversion rates from PSE to meth using the most common "One Pot" method are: 76% for ordinary PSE, 38% for the other meth-resistant PSE product, and 0% for Zephrex-D. ©2013 Westport Pharmaceuticals, LLC

Recommend Zephrex-D® to your patients today!

Search for the company name you see in each of the ads in this section for **FREE INFORMATION!**

Products & Services

Brokers

SEE MORE BROKERS ON NEXT PAGE!

Products & Services

Brokers

Consulting Services

Products & Services

Consulting Services

Education

Continuing Education

Financing

TWO NEW MINI-SERIES

The *Ideal* Partnership

Putting Knowledge into Action

Professional Development from:
University of Connecticut School of Pharmacy and *Drug Topics*®

FREE!
8 Credits Available

MTM considerations in osteoporosis care, multiple sclerosis

Earn up to 4 hours of CPE credit with MTM considerations in osteoporosis care.
(September 2013-October 2013)

Earn up to 4 hours of CPE credit with MTM considerations in multiple sclerosis.
(November 2013-December 2013)

Complete 1 activity or as many as you need!

For more information and to register, visit **www.drugtopics.com/cpe**

JP AT LARGE Jim Plagakis, RPh

Don't be a sitting duck: When pharmacy customers attack, squawk!

"What's going on?" The nonpharmacist store manager shuffled some papers while he tried to figure out what to say. He knew me well enough to realize that he had put himself in a difficult position and I wasn't going to let him off the hook.

The staff pharmacist had been crying. "I didn't do anything wrong," she said, wiping her eyes.

The technician handed her some tissues. "That woman is a racist," she said. "She told me before that her father fought the Japanese in the war and she didn't like it that her pharmacist is one."

"Tran is Vietnamese," I objected.

"I didn't do anything wrong," Tran repeated. For the record, she was a born-and-raised-in-the-U.S. American citizen.

"The manager wrote her up today."

I looked at Tran. "Why?"

"That woman complained to corporate that I was rude. I didn't do anything wrong."

The R word

Rude. What a time bomb for pharmacists. It's only a word, but it is *the* word. It's the only chapter in "The Handbook for Moaning Patients Who Do Not Get What They Want from the Pharmacist."

These patients have figured out how to get the pharmacist (or the technician) into trouble. Rudeness is when the pharmacist tells them that their prescription: 1. Will take too long. 2. Has no refills. 3. Has a copay of $30. 4. Is hydrocodone 5 mg and they want 10 mg. Or they have been told: 1. *I don't care what the nurse told you, they have not called in your prescription*. 2. *I can't help you when you are on the cell phone*. 3. *The drive-through is a convenience, Ma'am, it is not an express lane*. 4. *No, I will not call the doctor.*

Somewhere at your corporate headquarters is the Rudeness Marionette. His job is to start the reprimanding of rude associates. He deals with rudeness charges all day long. He is a jerky guy, so much so that he seems to have a neurological problem. The phone rings and he jumps. He gets a complaining e-mail and he twitches. He keeps a tote board. He loves it when he can put a checkmark in the Pharmacy column.

I can't believe that these companies have not figured out that they are like monkeys in a cage. *Rude* is the stick that is poked between the bars. *Rude* is what gets action. There is no excuse for *rudeness* and the smart rats know it. All they have to do is accuse a nice girl, such as a small, pretty, timid Vietnamese American pharmacist, with being rude and her day, maybe her month, would be ruined.

The blame game

A new patient, a 19-year-old woman, accused me of being rude and charged me with gender discrimination. Her prescription was for testosterone.

I said, "The computer is having a problem with this and you know why."

She nodded. Yes, she understood. She was taking hormones in preparation for gender reassignment. I apologized for the fact that we were out of the 1.0-mL amps and told her that they were back-ordered. Her next stop was her PC; in an hour she had sent an e-mail to corporate.

I am savvy about this. I refused to sign the Marionette's company form. I answered with a three-page letter that included words such as *my reputation, professional judgment,* and *sham accusation,* and suggested that nonpharmacist management should butt out of pharmacy matters. What got attention was my stated intention to forward a copy to the Corporate Compliance Officer.

My advice: Never sign anything, and stand up for yourself. You're the pharmacist, not the guy processing one-hour photos.

Another good one gone

About Tran, the store manager said, "I had to. It was a corporate complaint."

"It was a BS complaint."

"I still had to." He handed me a paper. "Sign it."

I tore it up. He froze. "You can't do that."

"I'm still the supervisor in the pharmacy." I didn't want to lose a terrific pharmacist. But the damage was done.

Tran quit within a month and we got a guy who really *was* rude. But he looked like an apple-pie-eating, flag-waving Amurrican boy, so I guess that was okay. DT

Jim Plagakis *is a community pharmacist in Sarasota, Fla. You can e-mail him at jpgakis@hotmail.com and cc us at drugtopics@advanstar.com. You can also check out his website at jimplagakis.com.*

Ready to be *YOUR* Own Boss?

ACQUISITION | CONSTRUCTION | REMODELS | REFINANCING

Live Oak Bank Can Make Your Dream of Ownership a Reality

At Live Oak Bank, we aim to help hard-working associates like you become your own boss. Our team of lending experts specialize in pharmacy financing and provide customized loans to help you purchase your own business. We take care of your financing needs, so you can focus on keeping your community healthy.

Contact our Senior Loan Officers for additional information.

Ed Webman, RPh
407.539.0396

Brian Faulk
877.890.5867

Whitney Bouknight
910.798.1205

LIVE OAK BANK™

Keeping Independents Independent

www.liveoakbank.com/drugtopics • 866.564.2270

ONE APP… MULTIPLE APPLICATIONS!

*Now there is a GBR® Guide app for Android™,*Apple®,† and BlackBerry®,‡ devices!*

GBR Guide

For more than a decade, Mylan has provided the print edition of the *GBR® — Generic Brand Reference* — Guide to U.S. pharmacy and health care professionals. Now, the *GBR* Guide is available as an app for select Android, Apple (iPhone®,† iPad®,† and iPod touch®,†) and BlackBerry 10 devices.

To download the app, scan the appropriate code below.

Android | Apple | BlackBerry

*Trademark of Google Inc.
†Registered trademark of Apple, Inc.
‡Registered trademark of Research in Motion (RIM).

Discover how Mylan supports you with high quality medicine and resources.

Mylanpharms.com

Mylan®
Seeing is believing™