Drug Topics® July 2013

OVERSIGHT Should pharmacy boards regulate PBMs? 41

MED SAFETY How to address underdosing in obesity 50

Special Insert
READY FOR BIOSIMILARS?

Drug Topics®

VOL. 157 NO. 7

Voice of the Pharmacist

DrugTopics.com

July 2013

TACKLING HIV

Take advantage of this opportunity!

Most Medicare Part B patients who rely on mail order will need to find a new supplier.[2]

Make sure your pharmacy is ready to meet this added demand by stocking up on and recommending ACCU-CHEK products.

ACCU-CHEK Products by Roche Rank **"Highest in Customer Satisfaction with Blood Glucose Meters"[3]** —J.D. Power and Associates

ACCU-CHEK blood glucose products by Roche ranked highest in a study that included the factors of Ease of Use, Performance, Cost of Test Strips, and Training among others.

[1] Medicare Part B patients with supplemental insurance often have $0 out-of-pocket costs. Final out-of-pocket costs vary from plan to plan.
[2] Under the new Medicare National Mail-Order Program, only 18 contract suppliers will provide diabetes testing supplies through mail order.
[3] ACCU-CHEK products by Roche Diagnostics received the highest numerical score in the proprietary J.D. Power and Associates 2012 Blood Glucose Meter Satisfaction Study℠, based on 2,681 total responses measuring 4 providers. Proprietary study results are based on experiences and perceptions of consumerssurveyed October 2012. Your experiences may vary. Visit jdpower.com.

Roche

ACCU-CHEK®

OVERSIGHT Should pharmacy boards regulate PBMs? 41

MED SAFETY How to address underdosing in obesity 50

Special Insert
READY FOR BIOSIMILARS?

VOL. 157 NO. 7

Drug Topics®

Voice of the Pharmacist
DrugTopics.com
July 2013

TACKLING HIV

Get involved to identify, treat patients earlier

PAGE 44

CPE CREDIT: 2.0 ACPE

Regulatory and ethical issues in pain management Page 58

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

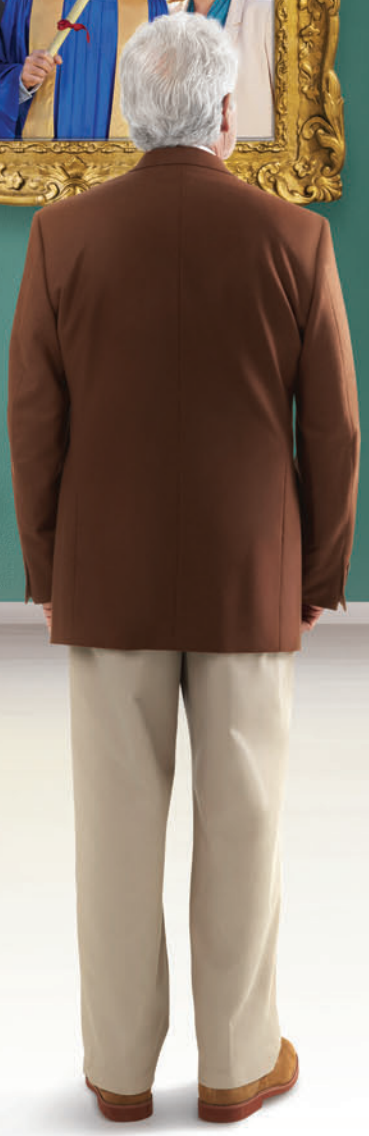
ADVANSTAR MEDICAL COMMUNICATIONS GROUP

facebook.com/DrugTopics
twitter.com/Drug_Topics

NEW

In moderate to severe Alzheimer's disease

Once-daily Namenda XR™ 28 mg+AChEI* demonstrated



Help slow symptom progression. Because there's so much to lose.

There is no evidence that NAMENDA XR or an AChEI prevents or slows the underlying disease process in patients with Alzheimer's disease.

NAMENDA XR™ (memantine hydrochloride) extended-release capsules are indicated for the treatment of moderate to severe dementia of the Alzheimer's type.

Dosage and Administration

- The recommended starting dose of NAMENDA XR is 7 mg once daily. The recommended target dose is 28 mg once daily. The dose should be increased in 7 mg increments to 28 mg once daily. The minimum recommended interval between dose increases is one week, and only if the previous dose has been well tolerated. The maximum recommended dose is 28 mg once daily.
- It is recommended that a patient who is on a regimen of 10 mg twice daily of NAMENDA tablets be switched to NAMENDA XR 28 mg once-daily capsules the day following the last dose of a 10 mg NAMENDA tablet. There is no study addressing the comparative efficacy of these 2 regimens.
- It is recommended that a patient with severe renal impairment who is on a regimen of 5 mg twice daily of NAMENDA tablets be switched to NAMENDA XR 14 mg once-daily capsules the day following the last dose of a 5 mg NAMENDA tablet.

Special Populations

- NAMENDA XR should be administered with caution to patients with severe hepatic impairment.
- A target dose of 14 mg/day is recommended in patients with severe renal impairment (creatinine clearance of 5-29 mL/min, based on the Cockcroft-Gault equation).

FOREST PHARMACEUTICALS, INC.
Subsidiary of Forest Laboratories, Inc.
St. Louis, Missouri 63045

063-14000090 04/13

improvements in cognition and global function[1]

- **In a 24-week study of 677 outpatients with moderate to severe AD on stable AChEI therapy, adding NAMENDA XR 28 mg was statistically significantly superior to placebo+AChEI (using an LOCF† analysis) in the co-primary endpoints of[1]:**
  - **— Cognition as measured by the Severe Impairment Battery (2.6 unit mean difference)[1]**
  - **— Global function as measured by the Clinician's Interview-Based Impression of Change (0.3 unit mean difference)[1]**
- **Studied in combination with leading AChEIs (donepezil, galantamine, or rivastigmine)[1]**
- **No titration required when switching from NAMENDA® (memantine HCl) to NAMENDA XR[1]**
- **The most commonly observed adverse reactions occurring at a frequency of at least 5% in NAMENDA XR-treated patients and at a higher frequency than placebo, respectively, were headache (6%, 5%), diarrhea (5%, 4%), and dizziness (5%, 1%)[1]**

Important Safety Information

Contraindications

- NAMENDA XR is contraindicated in patients with known hypersensitivity to memantine hydrochloride or to any excipients used in the formulation.

Warnings and Precautions

- NAMENDA XR should be used with caution under conditions that raise urine pH (including alterations by diet, drugs and the clinical state of the patient). Alkaline urine conditions may decrease the urinary elimination of memantine, resulting in increased plasma levels and a possible increase in adverse effects.
- NAMENDA XR has not been systematically evaluated in patients with a seizure disorder.

Adverse Reactions

- The most commonly observed adverse reactions seen in patients administered NAMENDA XR (28 mg/day) in a controlled clinical trial, defined as those occurring at a frequency of at least 5% in the NAMENDA XR group and at a higher frequency than placebo were headache (6% vs 5%), diarrhea (5% vs 4%), and dizziness (5% vs 1%).

Drug Interactions

- No drug-drug interaction studies have been conducted with NAMENDA XR, specifically. The combined use of NAMENDA XR with other NMDA antagonists (amantadine, ketamine, or dextromethorphan) has not been systematically evaluated and such use should be approached with caution.

*AChEI=acetylcholinesterase inhibitor.

†LOCF=last observation carried forward.

For more details, please visit **www.NamendaXRHCP.com**.

Please see brief summary of Prescribing Information on the following page.

Reference: 1. NAMENDA XR™ (memantine HCl) Prescribing Information. Forest Pharmaceuticals, Inc., St Louis, MO.

NEW
Once-Daily

Namenda XR™
(memantine HCl) extended release capsules
7 mg, 14 mg, 21 mg, 28 mg

NAMENDA XR (memantine hydrochloride) extended release capsules
Brief Summary of full Prescribing Information
Initial U.S. Approval: 2003

INDICATIONS AND USAGE: NAMENDA XR (memantine hydrochloride) extended-release capsules are indicated for the treatment of moderate to severe dementia of the Alzheimer's type.

CONTRAINDICATIONS: Hypersensitivity - NAMENDA XR is contraindicated in patients with known hypersensitivity to memantine hydrochloride or to any excipients used in the formulation *[*See *Description in the full Prescribing Information].*

WARNINGS AND PRECAUTIONS: Genitourinary Conditions - Conditions that raise urine pH may decrease the urinary elimination of memantine resulting in increased plasma levels of memantine. **Seizures -** NAMENDA XR has not been systematically evaluated in patients with a seizure disorder. In clinical trials of memantine, seizures occurred in 0.3% of patients treated with memantine and 0.6% of patients treated with placebo.

ADVERSE REACTIONS: Clinical Trial Data Sources - NAMENDA XR was evaluated in a double-blind placebo-controlled trial treating a total of 676 patients with moderate to severe dementia of the Alzheimer's type (341 patients treated with NAMENDA XR 28 mg/day dose and 335 patients treated with placebo) for a treatment period up to 24 weeks. 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. **Adverse Reactions Leading to Discontinuation -** In the placebo-controlled clinical trial of NAMENDA XR [See *Clinical Studies in the full Prescribing Information*], which treated a total of 676 patients, the proportion of patients in the NAMENDA XR 28 mg/day dose and placebo groups who discontinued treatment due to adverse events were 10.0% and 6.3%, respectively. The most common adverse reaction in the NAMENDA XR treated group that led to treatment discontinuation in this study was dizziness at a rate of 1.5%. **Most Common Adverse Reactions -** The most commonly observed adverse reactions seen in patients administered NAMENDA XR in the controlled clinical trial, defined as those occurring at a frequency of at least 5% in the NAMENDA XR group and at a higher frequency than placebo were headache, diarrhea and dizziness. Table 1 in the full Prescribing Information lists treatment-emergent adverse reactions that were observed at an incidence of 2% in the NAMENDA XR treated group and occurred at a rate greater than placebo. The first value displays the percentage of patients in the placebo group (N=335) and the second shows the percentage in the group receiving 28 mg of NAMENDA XR (N=341). **Gastrointestinal Disorders:** Diarrhea (4%, 5%), Constipation (1%, 3%), Abdominal pain (1%, 2%), Vomiting (1%, 2%); **Infections and infestations:** Influenza (3%, 4%); **Investigations:** Weight, increased (1%, 3%); **Musculoskeletal and connective tissue disorders:** Back pain (1%, 3%); **Nervous system disorders:** Headache (5%, 6%), Dizziness (1%, 5%), Somnolence (1%, 3%); **Psychiatric disorders:** Anxiety (3%, 4%), Depression (1%, 3%), Aggression (1%, 2%); **Renal and urinary disorders:** Urinary incontinence (1%, 2%); **Vascular disorders:** Hypertension (2%, 4%), Hypotension (1%, 2%). **Vital Sign Changes -** NAMENDA XR and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, diastolic blood pressure, and weight) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. There were no clinically important changes in vital signs in patients treated with NAMENDA XR. A comparison of supine and standing vital sign measures for NAMENDA XR and placebo in Alzheimer's patients indicated that NAMENDA XR treatment is not associated with orthostatic changes. **Laboratory Changes -** NAMENDA XR and placebo groups were compared with respect to (1) mean change from baseline in various serum chemistry, hematology, and urinalysis variables and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in laboratory test parameters associated with NAMENDA XR treatment. **ECG Changes -** NAMENDA XR and placebo groups were compared with respect to (1) mean change from baseline in various ECG parameters and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in ECG parameters associated with NAMENDA XR treatment. **Other Adverse Reactions Observed During Clinical Trials of NAMENDA XR -** Following is a list of treatment-emergent adverse reactions reported from 750 patients treated with NAMENDA XR for periods up to 52 weeks in double-blind or open-label clinical trials. The listing does not include those events already listed in Table 1, those events for which a drug cause was remote, those events for which descriptive terms were so lacking in specificity as to be uninformative, and those events reported only once which did not have a substantial probability of being immediately life threatening. Events are categorized by body system. **Blood and Lymphatic System Disorders:** anemia. **Cardiac Disorders:** bradycardia, myocardial infarction. **Gastrointestinal Disorders:** fecal incontinence, nausea. **General Disorders:** asthenia, fatigue, gait disturbance, irritability, peripheral edema, pyrexia. **Infections and Infestations:** bronchitis, nasopharyngitis, pneumonia, upper respiratory tract infection, urinary tract infection. **Injury, Poisoning and Procedural Complications:** fall. **Investigations:** weight decreased. **Metabolism and Nutrition Disorders:** anorexia, dehydration, decreased appetite, hyperglycemia. **Musculoskeletal and Connective Tissue Disorders:** arthralgia, pain in extremity. **Nervous System Disorders:** convulsion, dementia Alzheimer's type, syncope, tremor. **Psychiatric Disorders:** agitation, confusional state, delirium, delusion, disorientation, hallucination, insomnia, restlessness. **Respiratory, Thoracic and Mediastinal Disorders:** cough, dyspnea. **Memantine Immediate Release Clinical Trial and Post Marketing Spontaneous Reports -** The following additional adverse reactions have been identified from previous worldwide experience with memantine (immediate release) use. These adverse reactions have been chosen for inclusion because of a combination of seriousness, frequency of reporting, or potential causal connection to memantine and have not been listed elsewhere in labeling. However, because some of these adverse reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship between their occurrence and the administration of memantine. These events include: **Blood and Lymphatic System Disorders:** agranulocytosis, leukopenia (including neutropenia), pancytopenia, thrombocytopenia, thrombotic thrombocytopenic purpura. **Cardiac Disorders:** atrial fibrillation, atrioventricular block (including 2nd and 3rd degree block), cardiac failure, orthostatic hypotension, and torsades de pointes. **Endocrine Disorders:** inappropriate antidiuretic hormone secretion. **Gastrointestinal disorders:** colitis, pancreatitis. **General disorders and administration site conditions:** malaise, sudden death. **Hepatobiliary Disorders:** hepatitis (including abnormal hepatic function test, cytolytic and cholestatic hepatitis), hepatic failure. **Infections and infestations:** sepsis. **Investigations:** electrocardiogram QT prolonged, international normalized ratio increased. **Metabolism and Nutrition Disorders:** hypoglycaemia, hyponatraemia. **Nervous System Disorders:** convulsions (including grand mal), cerebrovascular accident, dyskinesia, extrapyramidal disorder, hypertonia, loss of consciousness, neuroleptic malignant syndrome, Parkinsonism, tardive dyskinesia, transient ischemic attack. **Psychiatric Disorders:** hallucinations (both visual and auditory), restlessness, suicidal ideation. **Renal and Urinary Disorders:** acute renal failure (including abnormal renal function test), urinary retention. **Skin Disorders:** rash, Stevens Johnson syndrome. **Vascular Disorders:** pulmonary embolism, thrombophlebitis, deep venous thrombosis. The following adverse events have been reported to be temporally associated with memantine treatment and are not described elsewhere in the product labeling: aspiration pneumonia, bone fracture, carpal tunnel syndrome, cerebral infarction, chest pain, cholelithiasis, claudication, depressed level of consciousness (including rare reports of coma), dysphagia, encephalopathy, gastritis, gastroesophageal reflux, intracranial hemorrhage, hyperglycemia, hyperlipidemia, ileus, impotence, lethargy, myoclonus, supraventricular tachycardia, and tachycardia. However, there is again no evidence that any of these additional adverse events are caused by memantine.

DRUG INTERACTIONS: No drug-drug interaction studies have been conducted with NAMENDA XR, specifically. **Use with other N-methyl-D-aspartate (NMDA) Antagonists -** The combined use of NAMENDA XR with other NMDA antagonists (amantadine, ketamine, and dextromethorphan) has not been systematically evaluated and such use should be approached with caution. **Effect of Memantine on the Metabolism of Other Drugs -** *In vitro* studies conducted with marker substrates of CYP450 enzymes (CYP1A2, -2A6, -2C9, -2D6, -2E1, -3A4) showed minimal inhibition of these enzymes by memantine. In addition, *in vitro* studies indicate that at concentrations exceeding those associated with efficacy, memantine does not induce the cytochrome P450 isozymes CYP1A2, -2C9, -2E1 and -3A4/5. No pharmacokinetic interactions with drugs metabolized by these enzymes are expected. Pharmacokinetic studies evaluated the potential of memantine for interaction with donepezil (See *Use with Cholinesterase Inhibitors*) and bupropion. Coadministration of memantine with the AChE inhibitor donepezil HCl does not affect the pharmacokinetics of either compound. Memantine did not affect the pharmacokinetics of the CYP2B6 substrate bupropion or its metabolite hydroxybupropion. **Effect of Other Drugs on Memantine -** Memantine is predominantly renally eliminated, and drugs that are substrates and/or inhibitors of the CYP450 system are not expected to alter the pharmacokinetics of memantine. A clinical drug-drug interaction study indicated that bupropion did not affect the pharmacokinetics of memantine. **Drugs Eliminated via Renal Mechanisms -** Because memantine is eliminated in part by tubular secretion, coadministration of drugs that use the same renal cationic system, including hydrochlorothiazide (HCTZ), triamterene (TA), metformin, cimetidine, ranitidine, quinidine, and nicotine, could potentially result in altered plasma levels of both agents. However, coadministration of memantine and HCTZ/TA did not affect the bioavailability of either memantine or TA, and the bioavailability of HCTZ decreased by 20%. In addition, coadministration of memantine with the antihyperglycemic drug Glucovance® (glyburide and metformin HCl) did not affect the pharmacokinetics of memantine, metformin and glyburide. Furthermore, memantine did not modify the serum glucose lowering effect of Glucovance®, indicating the absence of a pharmacodynamic interaction. **Drugs That Make the Urine Alkaline -** The clearance of memantine was reduced by about 80% under alkaline urine conditions at pH 8. Therefore, alterations of urine pH towards the alkaline condition may lead to an accumulation of the drug with a possible increase in adverse effects. Urine pH is altered by diet, drugs (e.g. carbonic anhydrase inhibitors, sodium bicarbonate) and clinical state of the patient (e.g. renal tubular acidosis or severe infections of the urinary tract). Hence, memantine should be used with caution under these conditions. **Drugs Highly Bound to Plasma Proteins -** Because the plasma protein binding of memantine is low (45%), an interaction with drugs that are highly bound to plasma proteins, such as warfarin and digoxin, is unlikely [See *Drug Interactions*]. **Use with Cholinesterase Inhibitors -** Coadministration of memantine with the AChE inhibitor donepezil HCl did not affect the pharmacokinetics of either compound. In a 24-week controlled clinical study in patients with moderate to severe Alzheimer's disease, the adverse event profile observed with a combination of memantine immediate-release and donepezil was similar to that of donepezil alone.

USE IN SPECIFIC POPULATIONS: Pregnancy - Pregnancy Category B: There are no adequate and well-controlled studies of NAMENDA XR in pregnant women. NAMENDA XR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Memantine given orally to pregnant rats and pregnant rabbits during the period of organogenesis was not teratogenic up to the highest doses tested (18 mg/kg/day in rats and 30 mg/kg/day in rabbits, which are 6 and 21 times, respectively, the maximum recommended human dose [MRHD] on a mg/m^2 basis). Slight maternal toxicity, decreased pup weights and an increased incidence of non-ossified cervical vertebrae were seen at an oral dose of 18 mg/kg/day in a study in which rats were given oral memantine beginning pre-mating and continuing through the postpartum period. Slight maternal toxicity and decreased pup weights were also seen at this dose in a study in which rats were treated from day 15 of gestation through the post-partum period. The no-effect dose for these effects was 6 mg/kg, which is 2 times the MRHD on a mg/m^2 basis. **Nursing Mothers -** It is not known whether memantine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when memantine is administered to a nursing mother. **Pediatric Use -** The safety and effectiveness of memantine in pediatric patients have not been established.

DRUG ABUSE AND DEPENDENCE: Memantine is not a controlled substance. Memantine is a low to moderate affinity uncompetitive NMDA antagonist that did not produce any evidence of drug-seeking behavior or withdrawal symptoms upon discontinuation in 3,254 patients who participated in clinical trials at therapeutic doses. Post marketing data, outside the U.S., retrospectively collected, has provided no evidence of drug abuse or dependence.

OVERDOSAGE: Signs and symptoms most often accompanying overdosage with other formulations of memantine in clinical trials and from worldwide marketing experience, alone or in combination with other drugs and/or alcohol, include agitation, asthenia, bradycardia, confusion, coma, dizziness, ECG changes, increased blood pressure, lethargy, loss of consciousness, psychosis, restlessness, slowed movement, somnolence, stupor, unsteady gait, visual hallucinations, vertigo, vomiting, and weakness. The largest known ingestion of memantine worldwide was 2 grams in an individual who took memantine in conjunction with unspecified antidiabetic medications. This person experienced coma, diplopia, and agitation, but subsequently recovered. One patient participating in a NAMENDA XR clinical trial unintentionally took 112 mg of NAMENDA XR daily for 31 days and experienced an elevated serum uric acid, elevated serum alkaline phosphatase, and low platelet count. No fatalities have been noted with overdoses of memantine alone. A fatal outcome has very rarely been reported when memantine has been ingested as part of overdosing with multiple drugs; in those instances, the relationship between memantine and a fatal outcome has been unclear. Because strategies for the management of overdose are continually evolving, it is advisable to contact a poison control center to determine the latest recommendations for the management of an overdose of any drug. As in any cases of overdose, general supportive measures should be utilized, and treatment should be symptomatic. Elimination of memantine can be enhanced by acidification of urine.

Manufactured for:
Forest Pharmaceuticals, Inc.
Subsidiary of Forest Laboratories, Inc.
St. Louis, MO 63045

Manufactured by:
Forest Laboratories Ireland Ltd

Licensed from Merz Pharmaceuticals GmbH

Revised: April 2013

62-12000315-BS-A-RMC8791-APR13

Please also see full Prescribing Information at www.namendaxr.com

Drug Topics®

EDITORIAL ADVISORY BOARD

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 Phil Molinaro
(732) 346-3074 / pmolinaro@advanstar.com

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

ACCOUNT MANAGER, RECRUITMENT ADVERTISING Jacqueline Moran
(800) 225-4569, ext. 2762 / jmoran@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

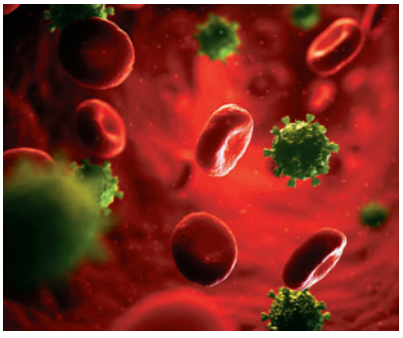
Michael Bernstein
VICE-PRESIDENT, LEGAL

J Vaughn
VICE-PRESIDENT, ELECTRONIC INFORMATION TECHNOLOGY

July 2013 **Drug Topics**® Voice of the Pharmacist DrugTopics.com Vol. 157 No. 7

COVER STORY

Tackling HIV



Despite the progress made in HIV/AIDS management, only 1 out of every 4 persons living with HIV achieves the goal of viral suppression. Pharmacists must be integral members of the healthcare team to help reverse this trend. **PAGE 44**

PRESCRIBED READING

GENERICS SUPPLEMENT

Ben Culpepper, PharmD
A clinical opportunity **PAGE 8**

Mike Lahr, PharmD
A few little words **PAGE 13**

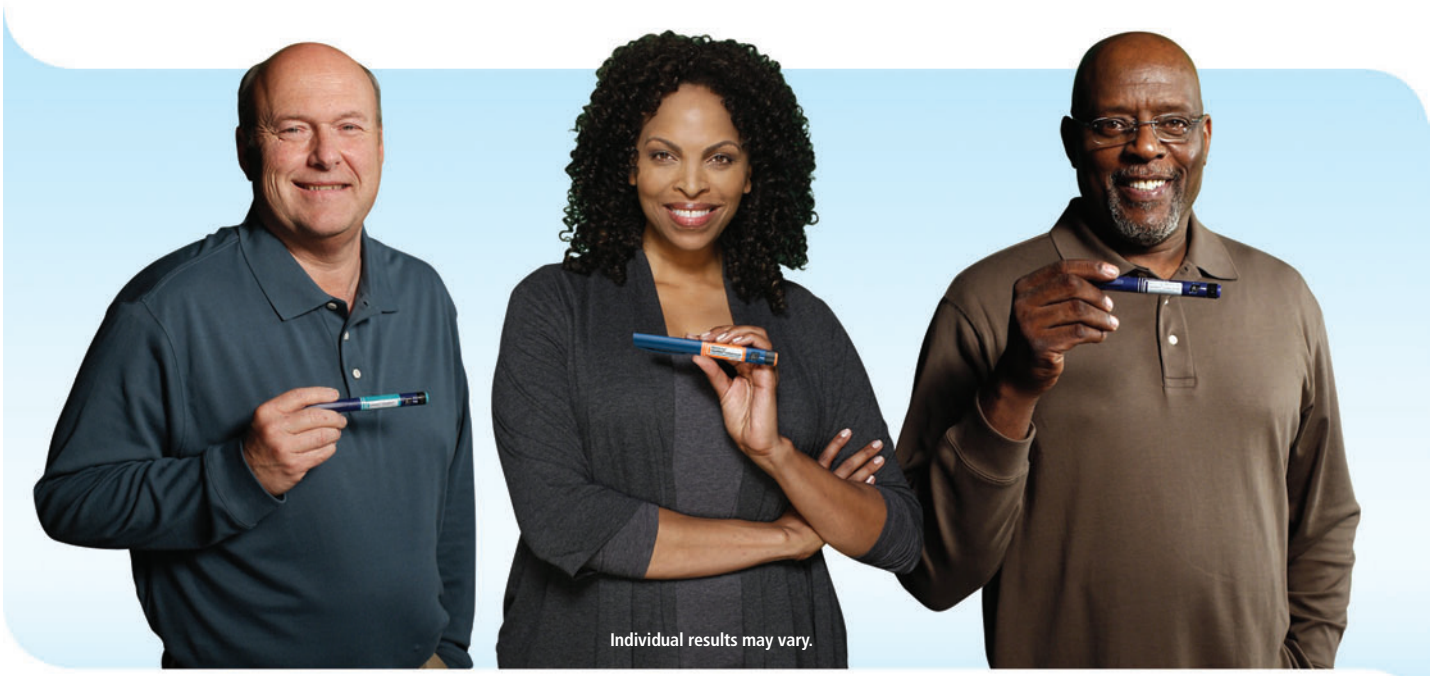
Michael J. Schuh, PharmD
Provider status now **PAGE 18**

Ned Milenkovich, PharmD, JD
Track and trace bill **PAGE 67**

Jim Plagakis, RPh
Pharmacognosy elective **PAGE 76**

GETTY IMAGES/SCIEPRO/SCIENCE PHOTO LIBRARY

Talk to your patients about **FlexPen®**, the only prefilled pen available with basal, bolus, and premix insulin analogs



FlexPen® is covered under most managed care plans for the same co-pay as vial and syringe*

FlexPen® is compatible with **NovoFine® 32G Tip** [6mm] disposable needles, our thinnest needle (Also available in 30G [8mm])

Don't forget to dispense NovoFine® needles

*Intended as a guide. Lower acquisition costs alone do not necessarily reflect a cost advantage in the outcome of the condition treated because there are other variables that affect relative costs. Formulary data are provided by Fingertip Formulary® and are current as of September 2012. Because formularies do change and many health plans offer more than one formulary, please check with the health plan directly to confirm coverage for individual patients. © 2012 Fingertip Formulary. All Rights Reserved.

Needles and FlexPen® must not be shared. Needles are sold separately and may require a prescription in some states.

novo nordisk®

Levemir®
insulin detemir (rDNA origin) injection

NovoLog®
insulin aspart (rDNA origin) injection

NovoLog® Mix 70/30
70% insulin aspart protamine suspension and 30% insulin aspart injection, (rDNA origin)

July 2013 **Drug Topics** Voice of the Pharmacist Vol. 157 No. 7

CPE **CONTINUING EDUCATION**

Regulatory, ethical issues

Learn how to minimize the risks of abuse, misuse, addiction, and diversion associated with opioid use in the treatment of pain.

PAGE 58

COUNTER POINTS

ISSUES & TRENDS

CHAINS AND BUSINESS

CLINICAL

REGULATORY & LEGAL

PRODUCT UPDATES

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

A work environment that breeds dissatisfaction
Wole Williams describes chain store pharmacy working conditions in detail, where pharmacists and pharmacy technicians are treated with little respect and work under deplorable conditions.

WEB EXCLUSIVES

Plan B One-Step available to all
http://drugtopics.com/PlanBOne-Step

Nexium alternative coming soon
http://drugtopics.com/Nexiumalternative

Diabetes linked to dementia?
http://drugtopics.com/diabetesdementia

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, PO. 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.

GETTY IMAGES / PHOTODISC / STEVE ALLEN

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

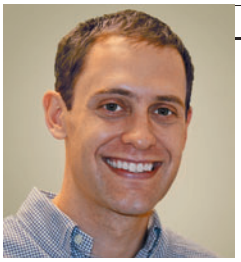
Brian Faulk
877.890.5867

Whitney Bouknight
910.798.1205

LIVE OAK BANK™

Keeping Independents Independent

www.liveoakbank.com/drugtopics • 866.564.2270



DISPENSED AS WRITTEN Ben Culpepper, PharmD; David D. Pope, PharmD, CDE

HIV: A clinical opportunity for the community pharmacist

Opportunities arise daily for community pharmacists to function as clinically as their hospital-based counterparts. Many pharmacies have begun to offer free blood pressure or blood sugar testing; some are even performing health screenings such as lipid panels and HIV screenings. Pharmacists are becoming leaders in diabetes or hypertension management and are proficient in discussing these subjects with their patients.

The services gap

As services for some disease states have flourished, those for other treatment areas such as oncology, mental health, and HIV/AIDS seem to have fallen by the wayside. The novel pharmacotherapy of these "complex" medical conditions may intimidate pharmacists. In practice, a pharmacist may receive prescriptions and simply accept them as correct, without being certain that the medications prescribed by the doctor are appropriate. In the case of HIV, many pharmacists may be confused by the extensive array of medications, the complex regimens, the question of whether a regimen is correct, or even the best way to counsel a patient in the use of these medications.

At present, there are 25 approved medications for the treatment of HIV/AIDS (not including the combination drugs such as Truvada or Stribild). These medications together make up six drug classes: nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (nNRTIs), protease inhibitors (PIs), fusion inhibitors, CCR5 inhibitors, and the new class of integrase inhibitors.

Remember, though, that in hypertension pharmacotherapy there are at least 12 classes of medications, including loop diuretics, thiazide diuretics, ACE inhibitors, ARBs, beta-blockers, two types of calcium channel blockers, etc. There are twice as many classes of antihypertensive drugs as there are classes to treat HIV/AIDS. And yet you learned everything you needed to know about every drug included in each class of hypertension agents.

Adding to the confusion connected with HIV medications is the fact that there are three names for each agent (trade name, generic name, and abbreviation). While this can seem daunting, it can be overcome, just as we have learned the brand and generic names for all the other medications and can recall them without much struggle.

Know your stuff

Another issue that arises in the management of HIV medications is that many pharmacists may not fully understand what constitutes an appropriate therapy regimen. There are many resources available online that offer quick and easy information to help determine the appropriateness of a regimen. For a credible resource on all available medications, a thorough pocket guide can be found under the Resources page at *www.fcaetc.org.*

Consider hypertension, for example. How many patients' conditions are currently controlled only by HCTZ or lisinopril? Or take the case of patients living with diabetes. How many of them are simply receiving metformin? The point is that all disease states have difficult, complex regimens. Pharmacists must take the time to learn the basics in every instance.

Knowledge is the pharmacist's first step toward becoming an active leader in the management of HIV medications. As the medication expert of the healthcare team, the pharmacist should be able to determine which medication goes in which class. Once this is achieved, it is much simpler to determine whether a regimen is appropriate or not.

The proverbial monkey wrench comes in when resistance develops and the traditional regimen is altered. For example,

Continued on pg. 17

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

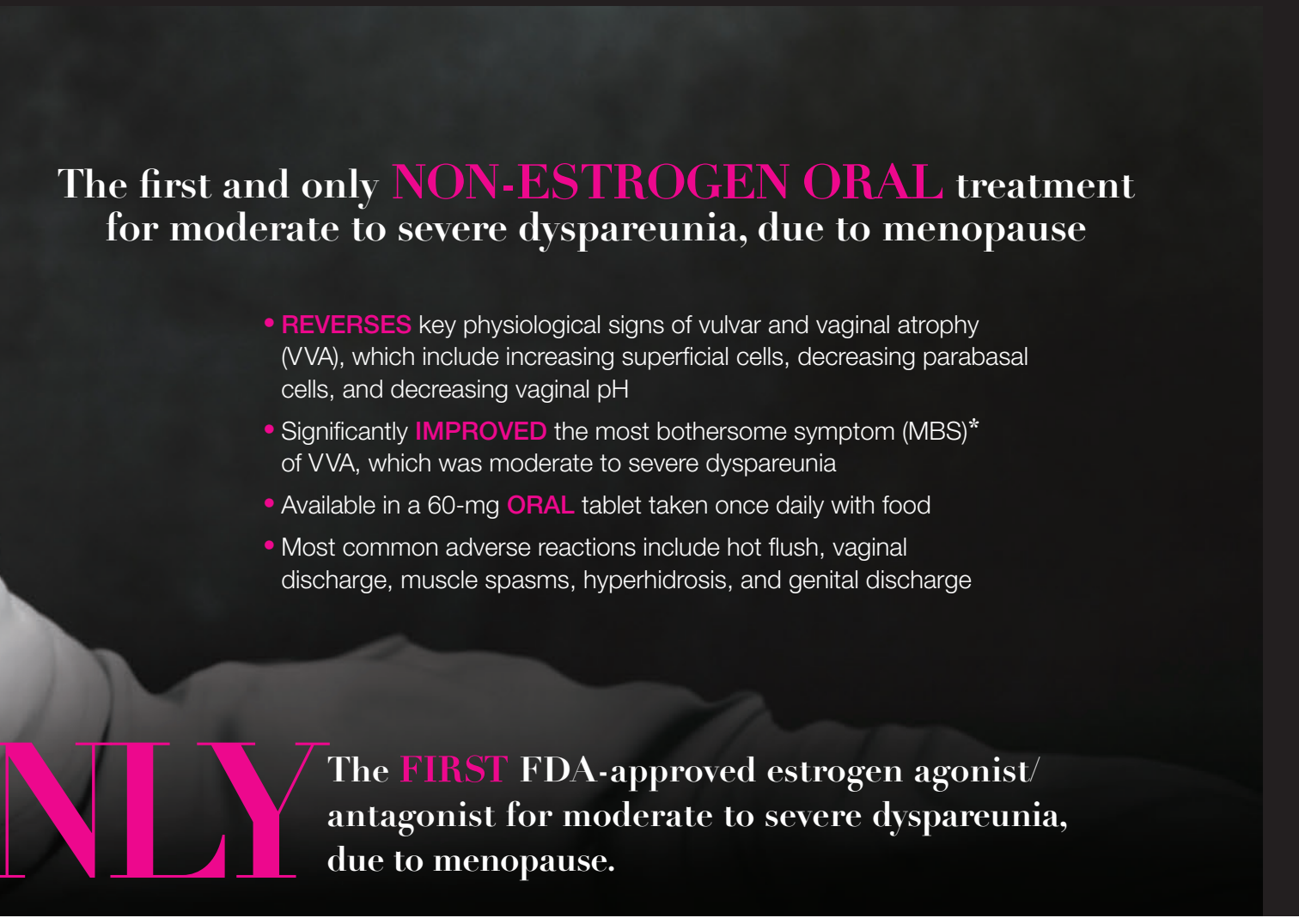
Osphena has not been adequately studied in women with breast cancer; therefore it should not be used in women with known or suspected breast cancer or with a history of breast cancer.

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.

IN MY VIEW Mike Lahr, BS Pharm, PharmD

The few words that change everything

I turned 60 this year. It gave me reason to pause and reflect on my life and my career. I did not remember days, I did not remember months, I did not remember years; I remembered select moments within them. What flashed across my mind was the faces of those I have known and worked with. I remembered times when people told me in either word or deed that I mattered. I found myself writing letters of thanks for those simple words spoken to me, for the simple things people did that made an impression on me.

The things that stick

We spend more time at work than anywhere else. In our world of science and medicine, we busy ourselves with clinical programs, advanced degrees, research accomplishments, continuous quality improvement, successful marketing, and all the rest. In the final analysis, how much does all that matter?

From my vantage point I can assure you that as you near the end of your career, it is the people you met along the way that you will value, not the things you did. There is a world of difference between saying to a colleague, "That was good work," and saying, "You matter to me." Which would you rather hear? Which will you remember decades from today?

View from the passenger seat

I recall looking out the side window of the car when I was young. The images of light and dark and shadow and color would flash by so quickly that I could not interpret what I was seeing.

Day-to-day life is like that. So many things happen every day. Most of them fade into glimpses and blurs of forgotteness. A few last. A few stay with us for our entire lives.

When you arrive at the later decades of life, you will be able to list the times this happened to you. You too will marvel at the simplicity of events that turned out to be life-changing. You too will remember those few words that changed everything.

A few little words

The next things that came to mind as my thoughts unfolded were the times I had missed my chance to say something. I can remember each one all too clearly. We all have memories colored by regret, when we say to ourselves, "I wish I had said something."

How many stories have you heard of death-bed regrets for lost opportunity? How many times have you listened to the sad tale of parents and children who never spoke words of love? I cannot count the times I have heard the painful words, "I know my dad loved me, but he never told me."

We never know which conversation with a person will be our very last. Unexpected things happen every day. Our world is full of tragic and dramatic reminders that life is fragile and time is short. What will happen if your miss your chance? What if you don't initiate that moment? What happens if you do not take that risk?

I can truthfully tell you that you will never forget it. It will haunt you. It will follow you all your days.

It's your decision

When you reach the end of your career, I assure you, you will look back and care more about the people you encountered than about your professional accomplishments. You will value most the people you touched along the way. The moments of human contact and compassion are what you will treasure.

Every day you get to decide how you will use your time at work. If you alter your course ever so slightly, you will forever change those you encounter. If you initiate a sincere, truthful word of affirmation just once a day, it will completely change the content of your memories on that last day, when you walk out the door.

Make the opportunity. Take the initiative. Be sure to tell the people you care about how important they are to you.

Get busy; you don't have as much time as you think. DT

Mike Lahr *is a clinical pharmacist with Salem Hospital in Salem, Ore. He can be reached at mikelahr@aol.com.*

IN MY VIEW Benjamin Gibson, PharmD, CPhT

Pharmacy practice at the Indian Health Service: Visit notes

Recently, I had the opportunity to work in the McLaughlin, S.D. Indian Health Service (IHS) Clinic at the Standing Rock Indian reservation. In one way, the experience was different from any other I've had, in that no patients had to bring money to the pharmacy. All billing depended on the computer system's dispensing records.

Another novelty was the McKesson Drug-O-Matic pill-counting device, which I had never seen before. It could count up to a few thousand pills, although we normally dispensed about 90 pills.

As at a retail pharmacy, the clinic also dispensed condoms, supplements, and over-the-counter items.

Communication

The way the clinic was set up, prescribers' computers were arranged in an adjoining room. In the wall separating the prescribers from the pharmacy, there was a window through which the pharmacist and prescribers could talk. A door fitted into the window would be swung shut at the nightly closing of the pharmacy. Prescriptions were faxed to the nursing station and accepted through the window. The nurses also asked for such items as injections or a clonidine tablet for patient administration.

Sometimes drug-information questions came through the window, such as "Do you think this is a good course of therapy?" Why make a phone call when you can talk between walls?

Before any medication was dispensed, policy dictated that a note be completed in the patient's chart. Occasionally a patient would inquire about the status of a prescription. If the note was not yet finished, or if a question had been forgotten, it was easy to ask the prescriber for more information. And sometimes a provider requested orders verbally for quicker dispensing. Unfortunately, not all IHS clinics are designed to facilitate such easy communication.

Staff practices

The pharmacy took a daily half-hour lunch break, which allowed the staff to relax briefly. Generally the patients were aware of the policy and did not grouse about it.

The staff also limited service hours once a week in order to have time to complete paperwork and drug counts. The clinic sent the prescriptions in the mail. A weekly pizza accompanied an informal interdepartment meeting.

Patients were accustomed to leaving messages on the drug refill request line. The first few days I was there, I had to adjust to the reservation accent. Some of the locals would enter the pharmacy speaking Lakota. Upon seeing me, they would switch to English.

Normally medications were easily filled, unless they had been filled at a larger nearby facility earlier that day; the system would not allow for a refill of the same drug at a second site. One day, the system removed the number of refills that were available. To dispense the medication, the order was copied, adjusted, and refilled.

Occasionally, prescriptions for controlled medications were dropped off. If something seemed odd, the staff could check the state's Prescription Monitoring Program system.

Contract payment

When I first began at the clinic, I had to be fingerprinted at Fort Yates, which was a short drive from McLaughlin. This surprised me, because I had already been fingerprinted at the Veterans Affairs facility and as a student had to submit my fingerprints to FDA. However, within a few days I received my photo ID.

Before traveling to the reservation, I filled out forms acknowledging that I would be the subject of a background check. The forms were supposed to allow me to work until the background check was completed. However, a manager initially believed that I could not be paid for my work until the background check was finished. This caused some frustration for staffers who wanted me to work, but did not want me to work without pay. Another staffer wondered why I had not been ordered home if my background check was not complete.

Recalls

During my time at McLaughlin a drug recall occurred that concerned a flaw in an outer pill covering. Although we carried the product, the recall was specific to a large bottle size that we did not carry. Thus, we did not need to package up the pills and dispatch them in the postage-paid envelope. DT

Robert Gibson *is a pharmacist with RX Pro Health in Fort Hood, Texas. Contact him at bgibson1@gmail.com.*

HIV: A clinical opportunity for the community pharmacist

Continued from pg. 8

some patients may be on one NRTI, one nNRTI, and one PI — or they could be on two NRTIs only. Still other patients may be on salvage therapy and receiving two NRTIs, one nNRTI, one PI, and an integrase inhibitor. When these unusual regimens appear, the best practice is to call the doctor and confirm that the regimen is correct.

Which is worse: Taking a few minutes to call the doctor and get the patient on the correct medications to help control his or her disease, or just assuming that it is correct and letting the patient walk out the door with an inappropriate regimen?

Another way that the community pharmacist can make a significant impact in connection with HIV is through knowledge of basic counseling points that come with these medications. Reminding patients to take their efavirenz (Sustiva) at night or avoiding PPIs with atazanavir (Reyataz) can go a very long way.

When pharmacists counsel patients on these medications, it is very important to continue to give them positive reinforcement. One of the most important issues to discuss with patients in connection with HIV medications is adherence. Stressing that patients remain adherent is a simple thing, but it can have a critical effect on a patient's prognosis.

Consider offering feedback to physicians on patients who may not be taking their medications appropriately. Be sure to take action to determine reasons for nonadherence.

As the healthcare system continues to evolve, pharmacists have many opportunities to interact with patients and make a positive impact on their health, and they can play an active role in the treatment of patients with HIV. So the next time you refill the prescription for Truvada, take a second and think, "Is this the correct medication? Where is the rest of the drug regimen?" It could save a life. DT

Ben Culpepper *is the former PGY-2 community pharmacy resident with the University of Georgia College of Pharmacy and Barney's Pharmacy in Augusta, Ga. Currently, he is the PGY-2 community/academia pharmacy resident with Kerr Drug and the University of North Carolina School of Pharmacy in Chapel Hill, N.C. Contact him at ben.culpepper@gmail.com.* **David Pope** *is chief of innovation and co-founder of CreativePharmacist.com. Contact him at david@CreativePharmacist.com.*

IN MY VIEW Michael J. Schuh, BS, PharmD, MBA

Hey, got a few minutes?

What if 62,000 pharmacists appealed to their congressional representatives to create provider status for pharmacists? What if 62,000 pharmacists forwarded this message to two colleagues and they forwarded it to two colleagues and they did the same? Pretty easy and powerful message, huh? What if 62,000 pharmacists individually volunteered to visit with their congressional representatives or senators and/or their staffers to make the point personal? Wow! How powerful is that?

No more waiting for pharmacy leadership to do our bidding and then complaining about it. No more blaming others. We'll be able to sit back and say, "Yeah, I personally had something to do with that," to our children, our grandchildren, and most important, ourselves.

Go for the win

What would you like to see happen to our profession? What is the *most* important thing that could happen to elevate the profession from one of "product, then knowledge" to a profession of "knowledge, then product"?

Provider status. The ability to bill for services universally, divorced from product; to expand the practice of pharmacy further than it ever has been expanded.

We have a new healthcare bill that will stretch primary care givers to the limit, while leaving mostly idle the skills and knowledge of the most accessible asset the healthcare system has . . . the pharmacist. We must continue to educate our other medical colleagues about our skill sets, but more important, we must educate those who know the least about our skills: the lay public. And we must do so not only through our everyday activities but through the activities of those who enact the laws: Congress.

It can be a win/win situation. We take some of the heat off the stretched healthcare system, save on healthcare costs, and make our congressional representatives look good, all at the same time. But no one will know what we can do or how we can save the system unless we tell them. Most members of Congress are not medical professionals or even close to it. It will take our grassroots actions for them to understand how we can help.

Who, me?

You may be thinking, "Why should I get involved? I don't have time for this." Right? Do you have time to sit down and eat lunch or speak to a patient in depth about prescriptions? Does the prescription talk get abbreviated because it is not being paid for — unlike the act of filling an Rx or performing an immunization?

If you don't like something, do something about it in a meaningful and productive way. Prioritize what is important to you professionally, then act to make it better. Know that your expertise can help others in ways you could never imagine.

Act to make things better. Your expertise can help others in ways you could never imagine.

But for us to help others, the service must be paid for. It doesn't matter whether pharmacist services are provided by the government, a nonprofit, or a for-profit organization. They must be paid for with enough funds to generate incentive to provide these services — services that have been shown to reduce healthcare costs and extend the services of primary care providers who are already recognized under Medicare Part B and a multitude of other insurance plans.

Up to us

Why 62,000? That is the approximate membership of APhA, the largest of the professional pharmacy organizations. As a learned profession, we are primarily responsible for what we do, how we are perceived by the public, and how we can use our professional skills to help create healthier lives for our patients. Individually, we are all responsible as well.

I have just contacted both of my state senators (find yours at *http://www.senate.gov/)* and my congressional representative *(http://www.house.gov/)*. It took 15 minutes. Do you have 15 minutes? What are you waiting for? DT

Michael J. Schuh *is a clinical pharmacist in Jacksonville, Fla. He can be reached at SchwaRx1@comcast.net.*

Roche

Don’t gamble with your patients’ health.

24 blood glucose meters failed recent accuracy studies.* Is theirs one of them?

ACCU-CHEK® meters passed every study, ***every time.*** All other major manufacturers had a meter that failed.

Make the switch today.

The recent failure of a large number of blood glucose meters to consistently meet accuracy standards has created growing concern, especially for those using meters to determine how much insulin to dose. Your patients’ health is very important to us. It’s time to switch to an ACCU-CHEK meter today.

For more information, go to accu-chek.com/accurate

*Three studies evaluated meters using the global standard of ≥95% of individual glucose results from 3 test strip lots shall fall within ± 15 mg/dL of the results of the manufacturer’s reference method at glucose concentrations <100 mg/dL and within ± 15% at ≥100 mg/dL. Studies included: Freckmann G, et al. *J Diabetes Sci Technol.* 2012;6(5):1060-1075.; Baumstark A, et al. *J Diabetes Sci Technol.* 2012;6(5):1076-1086.; Brazg RL, et al. *J Diabetes Sci Technol.* 2013;7(1):144-152. Studies funded by grants from Roche Diagnostics.

ACCU-CHEK®

Voices

Moving on or staying put: A hard decision

Thanks for the great article (Put your money where your mouth is, David Stanley, RPh, June 2013, *Drug Topics*, page 18). Bravo to you and good luck! While I'm a hospital pharmacist, it is articles like this that prove to me my career choice long ago. In my area of the country, the independent, pharmacist-run shops are virtually nonexistent. I routinely get applications from retail "Big Box" pharmacists who seem burned out. I'm sending your article to one of my former technicians who just completed his second year of pharmacy school. He was going to be my summer intern, but was lured away by one of the major retail chains. I wished him good luck, but not goodbye!


Counter Points

VIEW FROM THE ZOO David Stanley, RPh

Put your money where your mouth is

I think it was the argument over the number of labels that could be on the pharmacy counter that did it. Actually, I'm pretty sure it was.

Mike Gillard, PharmD, BCPS
WHEATON FRANCISCAN HEALTHCARE – FRANKLIN HOSPITAL
MIDWEST ORTHOPEDIC SPECIALTY HOSPITAL
FRANKLIN, WISC.

A real eye opener

Thank you for comparing pharmacies to Dunkin' Donut shops (A word from PCMA, Mark Merritt, June 2013 *Drug Topics,* page 11). Nice one. Pretty classy coming from a Georgetown grad.

If you don't believe you can provide the PBM transparency the American people are asking for, then please provide the information to the employer groups you mention in your letter. Just take one of your Chesapeake Energy claims data reports and pull out, let's say, the levetiracetam prescriptions from the last year. Let their HR executives know how much you paid the pharmacy for the prescription and then tell them how much you charged Chesapeake.

Should be a real eye opener. I'll save a donut for you.

Joe Jeffries, RPh
ST. CLAIRSVILLE, OHIO

APhA calls for greater physician collaboration to combat Rx drug abuse

This week the American Medical Association House of Delegates adopted a resolution *(http://www.amednews.com/article/20130616/house/130619937/8/#inb2* – Resolution 218*)* calling "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." Such actions help call important attention to an issue, but don't address the real problem or offer solutions for patients and regulators.

The real problem is that the United States faces a major public health epidemic with prescription drug abuse, particularly opioid abuse. The problem is not that pharmacists are asking too many questions of their physician colleagues. That's just a symptom. The Drug Enforcement Agency (DEA) and other government entities have placed an increased, often unilateral burden and expectation on pharmacists to validate prescription orders received and medications dispensed in pharmacies.

Continued on pg. 29


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,

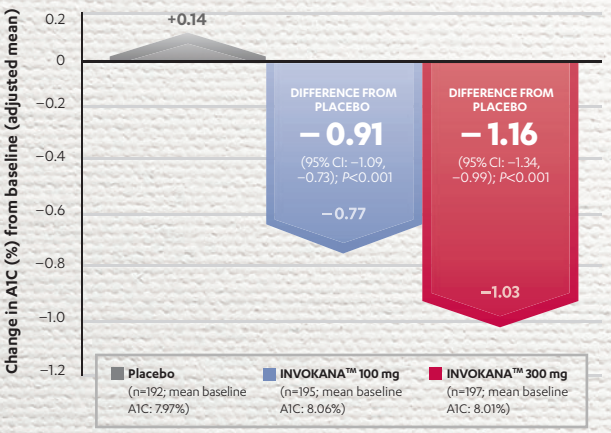
ENVISION NEW POSSIBILITIES

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]*.

Moving on or staying put

Continued from pg. 20

This pressure is largely due to concerns with substance abuse and growing public pressure to address the associated public health issues. Unfortunately, pharmacists do not typically have access to pertinent clinical information, so this management and verification process often requires reaching out to prescribers.

It is not pharmacy's intent to delay patients from receiving these needed medications or to unnecessarily interrupt prescribers. The current situation highlights the need for pharmacy, medicine, and regulators to collaborate on solutions that address the root cause of our healthcare system inefficiencies and abuse problems in this country.

While pharmacists are disappointed in the passage of a resolution that discourages a team-based approach to healthcare, the policy provides an opening to find solutions for controlled substance verification. These solutions need to incorporate changes to policy and health information technology.

The solution is truly more physician/pharmacist collaboration, not less. Pharmacists and physicians share the responsibility to ensure that controlled substance prescriptions are valid and appropriate and that patients understand the risks and benefits from the use of these medications. There are patients who legitimately need these controlled substance medications and all healthcare professionals should be united in advocating for those patients. Meanwhile, we also need improved government enforcement of the supply chain and support from practitioners in that effort.

Pharmacists are essential healthcare team members. We encourage physicians to continue working and talking with their patients' pharmacists. Open access and communication with the physician is vital to our patients' optimal health outcomes. We look forward to our continued discussions with the AMA on the pharmacist's responsibility to verify a prescription.

Thomas E. Menighan,
BS Pharm, MBA, ScD (Hon), FAPhA
EXECUTIVE VICE PRESIDENT AND CHIEF EXECUTIVE OFFICER
AMERICAN PHARMACISTS ASSOCIATION

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

Best eggs in the world

"So . . . What's it like?" The question is always delivered softly, with a tinge of hope. "You really bought your own drugstore?" I can hear them thinking. "Can pharmacists really own their own pharmacies in this day and age? After all, Rite Aid has over 4,000 of them, and the last recession they were within a whisker of a date in bankruptcy court. Can one of us really pull this off?"

"So . . . What's it like?" If I had a nickel for every time I've been asked, I'd have so much money I wouldn't have had to buy my place at all.

What it's like

I'll tell you what it's like. Imagine you're standing in front of a mountain of paper. You have a pen and a vague set of instructions. Your task is to fill out every page that makes up that mountain — correctly — or hire someone who can.

You know what? I take that back. It's more like a river. Think whitewater rafting in a river of paper, while you're holding a pen and filling out every page that goes by. And every time things start to calm down, someone asks about a form that was briefly mentioned long ago but is evidently very important and must be completed tomorrow.

In other words, it's a lot like pharmacy school. And same as with pharmacy school, when you successfully navigate your way through the ink and paper rapids, your reward is . . .

. . . The opportunity to start. By the way, that last form needed to be notarized. And you'll have to submit your passport photos again; something was wrong with the first set you sent out.

Imagine that being your day-in, day-out routine for around three months, and you'll have a little idea what it's like to get started owning your own pharmacy.

But then, when you're done, you might have a customer who regularly brings you eggs from his farm for no other reason than he's a nice guy. I have such a customer, and those eggs are worth more to me than any bonus I ever got killing myself for the chains.

What it's *not* like

I also can't count the number of times people have shaken my hand and welcomed me to town. Even my boss never shook my hand at my old chain gig.

My boss did smoke, though. She could have bought her cigarettes right in our store, and that says volumes about corporate pharmacy's commitment to its patients' health. I don't sell cigarettes, and I never will.

And I will never, ever, get a memo like this ever again:

*Subject: Pharmacy Service real time update *URGENT**
Date: Fri, 25 Mar 2011 10:20:12 -0400
From: XXxxxx@xxx.com
To:
Team 4,

- *We are self destructing this week on rx service!!!! 84.7; two days left let's pick it up TODAY!!*
- *59.2 on addressed by name, 63.6 on wait time- Are we serious??? Do you think I will accept results like this?*
- *Wake up and start delivering excellent service results NOW!!! You've worked too hard this month to throw it all away.*
- *If you're not able or willing to lead your team to deliver excellent service to each patient each time, please let me know so we can discuss your exit strategy- one thing I won't accept are poor service results; neither should you.*

That was an actual memo. Its recipient, who worked at another chain, forwarded it to me awhile back. And I know the only people who are surprised that this tone is taken with professionals with doctorate degrees are people who have never worked in a chain drugstore.

You'd like it too

So what's it like? To try and navigate a whitewater river of paper without a guide or map; to wake up each and every day to a new list of problems, large and small, that you can no longer kick upstairs? To have people's paychecks dependent on your making the right decisions?

It's . . . the most awesome feeling I've had in a long time. And I wouldn't trade it for the world.

Don't think you can't get that feeling as well. DT

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

FDA advisers recommend easing Avandia restrictions

FDA advisers recommended in early June the easing of restrictions on the diabetes drug rosiglitazone (Avandia, GlaxoSmithKline), following an independent reexamination of GSK's RECORD study conducted by Duke Clinical Research Institute.

In 2010, FDA limited patient access to the drug after concerns were raised about a possible increased risk of heart attacks connected with its use. It was banned in Europe.

During the latest joint meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee, most of the FDA advisers decided to modify (13) or remove (7) the Risk Evaluation and Mitigation Strategy (REMS) program after the independent study confirmed GSK's original findings, concluding that the risks of mortality or adverse cardiac outcomes with rosiglitazone used in combination with metformin or sulfonylurea are no different from those connected with the combination treatment of metformin and treatment with sulfonylurea only. However, five FDA advisers voted to keep the current REMS in place, and one adviser wanted to remove the drug from the market.

"We appreciate the committee's thorough examination of the RECORD results and will continue to work with FDA as it considers the recommendation of the committee," said Dr. James Shannon, GSK's chief medical officer.

The Duke Clinical Research Institute analyzed the RECORD trial data and found the hazard ratio for cardiovascular death, myocardial infarction, and stroke to be 0.95 (95% CI: 0.78-1.17), which is close to the hazard ratio from the original study of 0.93 (95% CI: 0.74-1.15).

FDA will be making its decision, now that the two committees have met and voted on the issue.

Majority of FDA advisers vote in favor of modifying or removing REMS program for rosiglitazone (Avandia, GlaxoSmithKline).

HEALTH PLAN PARTNER

Target works to improve Medicare Part D Star ratings

Retail pharmacies have a responsibility to improve Medicare Part D Star ratings – and partner with health plans to achieve those goals, according to an executive with Target.

Kevin Masci, group manager of Healthcare Safety and Quality at Target, shared the retailer's initiatives during the Pharmacy Quality Alliance's *Health Plan Strategies for Improvement of Medicare Star Ratings* webinar in June.

"Retailers are very well-positioned to improve the Star ratings. In retail pharmacy, we can drive the results and have the responsibility to help our payer partners achieve this," Masci said. "It's not just about Medicare. Many commercial lenders are interested in learning how we are driving out costs. Our offerings need to be simple, effective, and value-added, and we have to get the measurements to prove it," Masci said.

As a result, Target has implemented information management technology and medication therapy management (MTM) programs that Masci believes will help the retailer boost its Star ratings, provide more value to customers, and drive down costs.

Target's partnership with PQA's EQuIPP pilot program – a performance information management platform that will become commercially available – helped the retailer "understand pharmacy measurements and how we perform," Masci said.

Target's current test with EQuIPP in Florida will "give us a closer look at Medicare and commercial payer results in a robust market," according to Masci. "The testing at our Florida stores is a critical piece that helps us understand where the opportunities lie. In our Minnesota market, the program has been very well received by patients and pharmacists, and we are looking to expand it in a number of other markets very shortly," he said.

Target has also set an MTM pilot project in motion that will provide the retailer with a more structured clinical approach to drive better outcomes with patients' diabetes, hypertension, and other health conditions, according to Masci. "There is not a one-size-fits-all approach. We are implementing customization programs for patients," which can include text messages, Masci said.

It is essential that retailers, health plans, providers, and others collaborate to boost Star ratings and improve patient health outcomes. "We all have access to the critical pieces of data that are not always shared. It is hard to create that full picture of a patient," Masci said.

–Christine Blank, Contributing Editor

CIVIL PENALTIES

Walgreens agrees to pay $80 million in DEA settlement

Walgreens, the largest pharmacy chain in the United States, has agreed to pay $80 million in civil penalties for record-keeping and dispensing violations under the Controlled Substances Act, according to statements released June 11 by the company and the Drug Enforcement Agency (DEA).

The DEA settlement, the largest in the agency's history, resolves all pending litigation and requires that the pharmacy chain surrender its DEA registrations at 6 of its Florida pharmacies until May 2014 and at its Jupiter distribution center until September 2014. At the distribution center, Walgreens did not report to the DEA suspicious prescription drug orders that it received from its retail pharmacies, according to DEA.

The DEA stated that Walgreens had "an unprecedented number of record-keeping and dispensing violations under the Act," which resulted in oxycodone and other pain medications being diverted for abuse and illegal sale on the black market.

"Walgreens has agreed to enhance its training and compliance programs, and to no longer monetarily or otherwise compensate its pharmacists based on volume of prescriptions filled."
–Drug Enforcement Agency statement

"Walgreens' alleged failure to sufficiently report suspicious orders was a systematic practice that resulted in at least tens of thousands of violations and allowed Walgreens' retail pharmacies to order and receive at least three times the Florida average for drugs such as oxycodone," according to the DEA.

In addition to the civil penalty and the revoked DEA registrations, Walgreens has agreed to create a Department of Pharmaceutical Integrity to ensure compliance and prevent diversion of controlled substances, DEA said.

"Walgreens has also agreed to enhance its training and compliance programs, and to no longer monetarily or otherwise compensate its pharmacists based on the volume of prescriptions filled," according to DEA.

Kermit Crawford, Walgreens' president of pharmacy, health and wellness, said, "We are fully committed to doing our part to prevent prescription drug abuse. We also will continue to advocate for solutions that involve all parties . . . to play a role in finding practical solutions that combat the abuse of controlled substances and ensure patient access to critical medications."

DECLINE IN EFFICACY

New study: Newer drugs may offer slightly better results than placebo

The effectiveness of new drugs compared with that of older drugs has fallen since the 1970s, according to a new study in *Health Affairs*.

In the study, researchers randomly selected and analyzed the results of 315 clinical trials that compared a drug to a placebo from 4 medical journals: *New England Journal of Medicine, Journal of the American Medical Association, Lancet,* and *British Medical Journal* between 1966 and 2010.

The data extraction was done by research assistants who were kept blind to the purpose of the study and all studies were independently reviewed by 2 different research assistants. Drugs to treat cardiovascular disease, cancer, mental disorders, and respiratory illness were included.

"Medical breakthroughs of the sort that confer large benefits above placebo are becoming less common."

Researchers found that the average effect size, as measured by the odds ratio, decreased from a peak of 4.51 (1971-1980) to 1.36 (2001-2010).

"In other words, there has been a significant decline over time in the extent to which new drug treatments have been shown to be significantly more effective than placebos to the point that in recent years the average study found only small differences between the active drug and placebo," said lead author Mark Olfson, professor of clinical psychiatry at Columbia University and a research psychiatrist at the New York State Psychiatric Institute in New York City.

"The results suggest that medical breakthroughs of the sort that confer large benefits above placebo are becoming less common," said Dr. Olfson. "An awareness of the uncommonness of these transformational drug discoveries helps to calibrate expectations for future placebo-clinical trials.

"With apparently declining yield from placebo-controlled studies, now may be a good time to place greater emphasis on studies comparing 2 or more drugs that are known to be effective to evaluate whether there are meaningful differences between them in their tolerability, adherence, safety, or costs," Dr. Olfson said.

According to Randy Vogenberg, managing principal of Bentelligence, many plans and PBMs already have been looking to maximize generic therapies over the last few years. "As part of the riding the generic wave, plans and PBMs have become increasingly aggressive in promoting step therapy strategies as well as optimizing first-line generic-only treatments," he said.

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

AMERICA'S LEADING LICE BRAND
RID
FOR OVER 10 YEARS

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

BAYER

IMS REPORT

Responsible medication use key to lower healthcare costs

Delays in treatment and medication nonadherence are the major reasons behind avoidable costs in the healthcare system, according to a recently released study.

Avoidable costs of more than $200 billion are incurred each year in the U.S. healthcare system, representing 8% of the country's total annual healthcare expenditures, the IMS Institute for Healthcare Informatics found.

"This also translates to a significant cost to patients and unnecessary utilization of healthcare resources, including 400 million hospital visits annually. This could all be avoided if medicines were used more responsibly," Murray Aitkin, executive director of the IMS Institute for Healthcare Informatics, said on a conference call with media.

Medication nonadherence drives the largest avoidable cost – $105 billion annually – in U.S. healthcare, IMS found. Delays in applying evidence-based treatment to patients also results in $40 billion in annual avoidable costs. After reviewing four primary disease areas: Hepatitis C, type 2 diabetes, atrial fibrillation, and coronary heart disease (CHD), IMS found that the largest avoidable impact to the U.S. healthcare system is in the area of diabetes, where delays increased outpatient visits and hospitalizations.

In addition, the misuse of antibiotics contributes to antimicrobial resistance and an estimated $34 million each year in avoidable costs. An additional $1 billion is spent on about 31 million inappropriate antibiotics prescriptions that are dispensed each year, typically for viral infections, according to IMS.

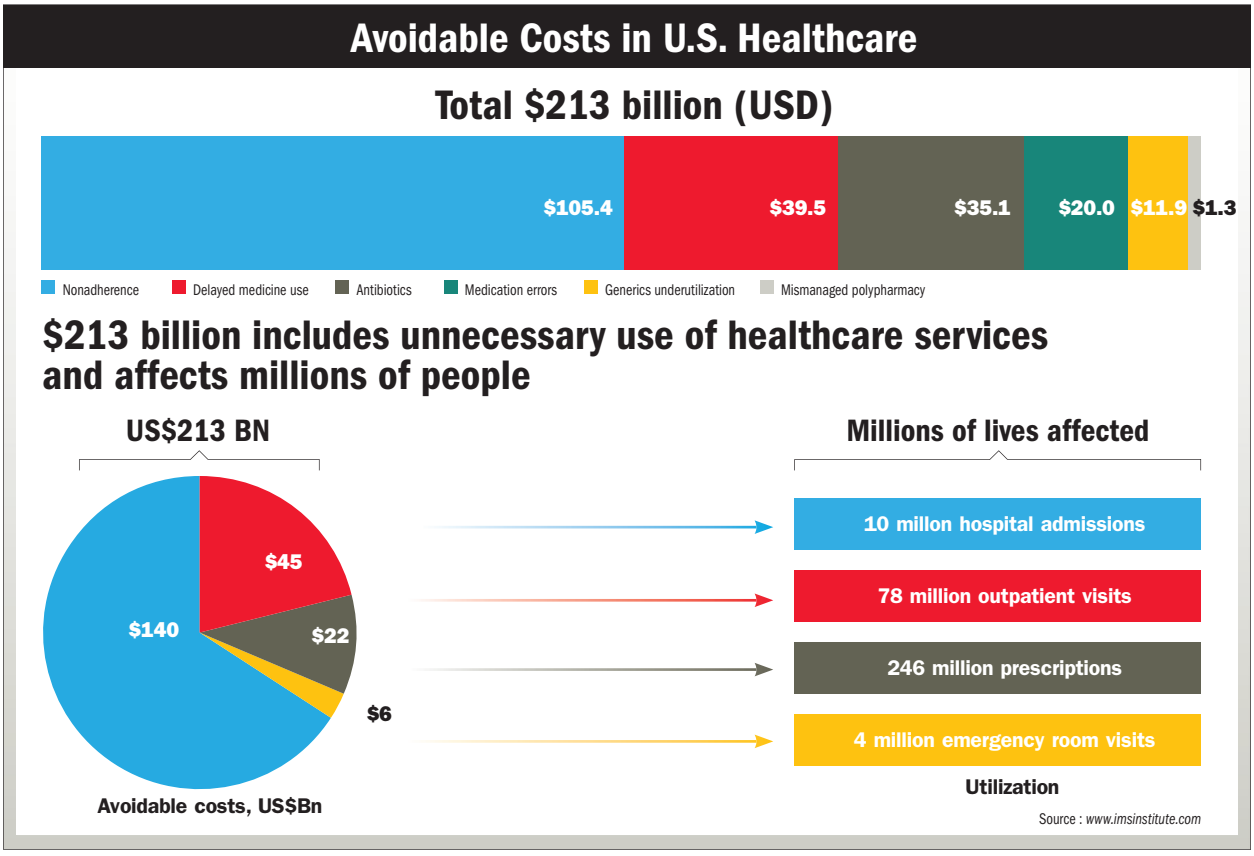
However, "there are encouraging signs that efforts to drive responsible antibiotics use are paying off, particularly in the declining number of prescriptions for the common cold and flu," according to a statement from IMS.

The IMS Institute for Healthcare Informatics also sees major improvements with medication adherence, which will drive down avoidable costs in the future. "The Affordable Care Act, including incentives for a performance-based payment system, and the introduction of the Accountable Care Organization, enables Medicare to really put a focus on helping support these areas. Adherence is clearly indicated in the ACO performance metric," Aitken said.

"Performance-based payments and a more integrated delivery of healthcare are elements that…will be positive forces in terms of addressing the avoidable costs we have described," Aitkin added.

Other factors driving U.S. healthcare costs include: Suboptimal use of generics, medication errors, and mismanaged polypharmacy, according to IMS.

–Christine Blank, Contributing Editor



Pharmacists Insights

What Patients with Diabetes Don't Know May be Hurting Them

Injectable diabetes medications are underutilized for a variety of reasons, including fear of needles or discomfort experienced with previous injections. Survey data suggest that one-third or more of patients with diabetes do not use insulin as prescribed, with a large subset of these patients intentionally skipping doses.[1] Individuals who do not initiate therapy or comply with their prescribed medication regimen are at elevated risk for neuropathy, retinopathy, cardiovascular disease, and other diabetes-related complications.

More Comfort, Less Risk

The introduction of shorter and smaller-gauge needles has the potential to change a patient's relationship with injectable medications. By improving comfort and reducing the risk of inadvertent intramuscular injection,[1,2] shorter needles may be viewed more favorably by patients. According to Devra Dang, PharmD, Associate Clinical Professor of Pharmacy Practice at the University of Connecticut School of Pharmacy, "Some patients experience more pain with the longer needles and find them more psychologically distressing. When given the choice, most patients prefer a shorter needle and a smaller needle gauge."

Dr. Dang

Newer recommendations regarding needle length have been shaped by the finding that skin thickness is generally less than 3 mm across populations and injection sites,[3] and by clinical trial evidence demonstrating comparable efficacy, safety, and tolerability with medication administered via shorter needles (i.e., 4 mm-6 mm) compared with their longer predecessors.[1,2] These data led the Third Injection Technique Workshop In Athens (T.I.T.A.N.) panel—a multinational conference of 127 physicians, nurses, diabetes educators, and psychologists—to conclude that the most recent recommendations and research substantiate that "There is no medical rationale for the use of needles greater than 6 mm in children and adolescents nor in adults."[2] This sentiment is echoed by the American Association of Diabetes Educators (AADE), which advocates the use of 4 mm to 6 mm needles for insulin injection in children and adolescents[1]—a group that experiences greater discomfort during injection and is prone to inadvertent intramuscular injection with longer needles.[1,2,4] Short and narrow gauge (4 mm x 32G) insulin pen needles were specifically highlighted by the AADE for their ability to reduce injection pain in both children and adults, including obese patients.

Know Your Needle Options

Healthcare practitioners have a wide variety of needle options when prescribing injectable diabetes medications, including innovative products such as the BD Ultra-Fine™ Nano™ 4 mm Pen Needles and BD Insulin Syringes with the BD Ultra-Fine™ 6 mm needle. The former is the smallest pen needle offered by BD and is even better now with EasyFlow™ Technology. Compatible with all diabetes pens sold in the US,* clinical studies have shown that these shorter needles are comparable in efficacy and tolerability with longer needles, yet reduce injection pain and improve comfort without increasing medication leakage.[5-7] BD Nano 4 mm Pen Needles offer improved comfort and ease of use; featuring a patented 5-bevel PentaPoint™ needle tip for easier insertion and an extra thin wall needle that improves the flow rate of insulin through the needle making it »

BD's patented 5-bevel needle tip is sculpted to create a flatter, thinner surface that helps penetrate the skin with significantly greater ease for a smoother and gentler injection.

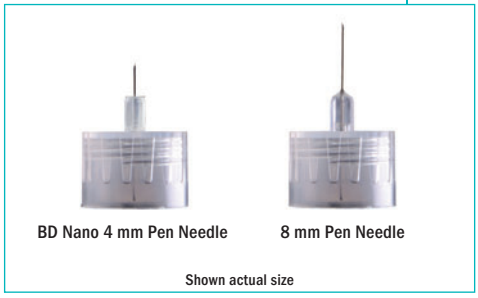
*As of August, 2012

6 Counseling Points for Your Patients with Diabetes

- Ask patients about their experiences with injectable diabetes medications. Pharmacists have the most contact with patients and should avail themselves of every opportunity to reassess a patient's injection needs and technique.
- Review the patient's refill history for signs of poor adherence. Issues with injection could be contributing to lack of medication compliance and longer term complications.
- Discuss shorter needle alternatives with patients currently using 8 mm or 12.7 mm needles. Patients may not know they have options. Even overweight or obese individuals are candidates for a 4 mm pen needle or 6 mm needle insulin syringe.
- Counsel both the patient and the prescriber. Offer to call the prescriber to change the patient's prescription if the patient expresses interest in a shorter needle.
- For those patients injecting with a syringe, let them know they too now have the option of injecting with a shorter needle — BD Insulin Syringes with the BD Ultra-Fine™ 6 mm needle.

easier for patients to press the pen's thumb button and complete an injection.[5,8]

The challenge for healthcare professionals is to tailor treatment to the patient's needs. "Oftentimes prescribers, especially primary care physicians, are not as familiar with the availability of all of the different lengths and gauges of the needles," explains Dr. Dang. "Community pharmacists have the best, most up-to-date information on that, so they can help both the patient and the prescriber pick the most appropriate insulin needle for the patient."



Consider providing an actual visual comparison to your patients, such as this 4 mm versus 8 mm pen needle.

Pharmacists are also an invaluable resource for patient education. Consultation with the pharmacist is an opportunity to discuss a patient's satisfaction with their current injection regimen, address any concerns, and relay information about the latest needle options. In fact, the T.I.T.A.N. panel recommends that "All patients should be apprised of the advantages of the shorter (4 mm-6 mm) length needles."[2] Injection technique is another essential component of the educational dialogue. The skin-fold pinch-up method may not be required for 4 mm and 5 mm needles, but the specifics of injection technique recommendations vary based on patient characteristics and injection site. Alternatively, it is important to counsel patients using needles ≥ 6mm about how to avoid intramuscular injections by holding the pinch-up until the needle is removed from the skin. It is important that patients are aware of these differences and adhere to proper injection technique.

Beginning the Conversation

Lastly, pharmacists are uniquely positioned to monitor for treatment adherence. Concern about adherence based on the patient's refill history provides a basis for the pharmacist to initiate a conversation with the patient about barriers to injectable medication use, including discomfort, pain, or needle phobia. This type of active approach is needed to help stem the tide of nonadherence to injectable diabetes therapies and its associated adverse sequelae. ■

Disclosures: Dr. Dang has no disclosures to report.

References

1. Siminerio L, et al. *Diabetes Educ*. 2011; 37 (Suppl 3):1-10. **2.** Frid A, et al. *Diabetes Metab*. 2010;36(Suppl 2):S3-S18. **3.** Gibney, MA, et al. *Curr Med Res Opin*. 2010;26:1519-1530. **4.** Lo Presti D, et al. *Pediatr Diabetes*. 2012;13: 525-533. **5.** Hirsch LJ, et al. *Curr Med Res Opin*. 2010;26:1531-1541. **6.** Hirsch LJ, et al. *Curr Med Res Opin*. 2012;28:1305-1311. **7.** Hirsch LJ, et al. *J Diabetes Sci Technol*. 2012;6:328-335. **8.** Aronson R., et al. *Clin Ther*. 2013., In Press, Corrected Proof, Available online 20 June 2013.

MEDICATION ADHERENCE

Prevention of heart attacks by targeting CVD patients

Face-to-face interaction between pharmacists and patients will be key to the success or failure of the federal government's Million Hearts initiative to prevent heart attacks and strokes, Salvatore Giorgianni, PharmD, told participants during the *State of Men's Heart Webinar* in June.

Giorgianni is a scientific advisor for Men's Health Network, which sponsored the webinar along with Million Hearts—an initiative by the Centers for Disease Control and Prevention (CDC) to avert 1 million heart attacks and strokes by 2017. Men's Health Network is encouraging providers to celebrate Men's Health Month this month, by participating in health screenings, health fairs, and other health education activities.

"Pharmacists can have a profound effect on the cardiovascular health of men and women in their communities."

"Pharmacists can have a profound effect and a profound impact on the cardiovascular health of men and women in their communities," Giorgianni said, noting historically poor compliance rates involving high blood pressure and high cholesterol medicines.

He urged pharmacists to build better relationships with providers, to offer targeted education and screening programs, and to red-flag patients receiving cardiovascular prescriptions for additional counseling. "It takes 2-3 minutes," he said. "That's all it really takes."

He pointed to studies such as the 1996 Asheville Project, which demonstrated that medical adherence rates rise dramatically and overall medical costs decline when pharmacists are involved in face-to-face consultations and follow-up.

"I talk to patients, when I'm doing [MTM], and they'll tell me 'I don't take that medication anymore. I don't have the condition anymore.' Many don't realize that these are medicines that they need to continue to take," Giorgianni said.

Thomas Frieden, MD, MPH, director, CDC, said 1 out of 3 men have some form of cardiovascular disease and 1,000 men die everyday due to heart attacks or strokes. "Too many men have some form of cardiovascular disease and are at risk," he said.

Frieden identified the two main causes of heart attacks and strokes in men as smoking and high blood pressure. He said the community portion of Million Hearts would focus on tobacco control, sodium reduction, and trans fat elimination.

Since many men are goal-orientated, Giorgianni suggested that pharmacists encourage male patients by pointing out successes. "Find something, anything, that they are doing right," he said. "Reinforce it."

–Mark Lowery, Content Editor

A WIN FOR CONSUMERS

SCOTUS splits on pay-for-delay deals

The U.S. Supreme Court has ruled for and against pay-for-delay deals between brand-name drug makers and their generic competitors.

In a 5-3 decision in June, the justices ruled that deals in which brand-name companies pay generic firms to delay entry of a cheaper version of the reference product are not inherently legal. The case was a win for the Federal Trade Commission, which has fought pay-for-delay for more than a decade.

Justices also ruled that pay-for-delay deals must be evaluated on a case-by-case basis and could be legal under some circumstances. That proviso could open the way for future pay-for-delay agreements.

Justice Samuel Alito recused himself from the case, Federal Trade Commission vs. Actavis, Inc. Et Al. The case involved an FTC challenge to a pay-for-delay agreement between Solvay Pharmaceuticals (now part of AbbVie), Actavis (formerly Watson Pharmaceuticals), Paddock Laboratories (now part of Perrigo), and Par Pharmaceuticals. Solvay challenged generic versions of its AndroGel (testosterone) in 2003, but settled in 2006 under a pay-for-delay deal. Solvay agreed to pay generic companies as much as $30 million yearly to not market their own testosterone gel products. The deal helped Solvay protect an estimated $125 million in annual profits from AndroGel.

"It clearly maps out how the FTC can use the law to stop these anticompetitive schemes and make sure consumers receive the full benefits."

The FTC sued in 2009, claiming the settlement violated antitrust laws. The district court dismissed the complaint. The 11th Circuit Court of Appeals rejected an appeal by FTC, which took the case to the Supreme Court.

"No other decision this term will have as much impact on consumer's pocketbooks," said former FTC Policy Director David Balto. "It clearly maps out how the FTC can use the law to stop these anticompetitive schemes and make sure consumers receive the full benefits of a competitive marketplace. At the same time, it permits the broad range of settlements that pose few competitive concerns."

FTC attorneys argued that pay-for-delay cost U.S. consumers $3.5 billion yearly in the form of higher prescription drug prices. The Supreme Court decision sends the case back to the lower courts. Both FTC and Actavis said they planned to continue the fight on the merits of the case.

–Fred Gebhart, Contributing Editor

Up front
In Depth

Mari Edlin, Contributing Editor

Should state pharmacy boards regulate pharmacy benefit managers?

Pharmacy benefit managers (PBMs) are concerned about states that are considering turning over the regulation of PBMs to state boards of pharmacy. Typically, state insurance commissions oversee PBMs. To date, only Mississippi has passed such legislation.

"State pharmacy boards comprised of pharmacists will be out for their own best interests since they compete with PBMs and their mail-order businesses," said Ed Buthusiem, director, Berkeley Research Group's Healthcare Practice in Washington, D.C. "Pharmacies could buy directly from manufacturers and drive drug costs up."

The debate continues

Buthusiem said the debate over the role of PBMs has been going on for a decade and he believes that most states will not pass a law giving state pharmacy boards authority for overseeing them.

"The boards should only be responsible for monitoring the behavior of pharmacists and licensing professionals in the discipline," he said.

Buthusiem is concerned that if boards assume oversight, PBMs will be required to disclose costs, and once that proprietary information is available, pharmacists will leverage it to their own competitive advantage.

Ironically, a 2006 survey by the International Foundation of Employee Benefit Plans found that 69% of plan sponsors using a PBM required their PBMs to pass through all manufacturer rebates, discounts, fees, and other payments. The survey also indicated that 63% of plan sponsors require an unrestricted right to audit their PBMs.

A conflict of interest

"It is a conflict of interest to be regulated by those with whom PBMs contract, those who negotiate their payments. It would open up a hornet's nest," said Mark Merritt, president and CEO of the Pharmaceutical Care Management Association (PCMA), the trade organization that represents PBMs.

PCMA threatened to sue Mississippi this year for attempting to push through additional regulations that would have imposed fiduciary mandates on PBMs and violated federal law. The state backed down. The initial regulation that allowed state boards of pharmacy to oversee PBMs passed in April 2011.

> **"It is a conflict of interest to be regulated by those with whom PBMs contract, those who negotiate their payments. It would open up a hornet's nest."**
>
> *–Mark Merritt, president and CEO, PCMA*

"We understand the need to be regulated, but we already are by state insurance commissioners," Merritt said. "Transferring responsibility to a board of pharmacy would only bring value to retailers. It may seem like a mom and apple pie scenario, but if you look more closely, retailers just want to increase their profits."

PCMA warned that the legislation is like "letting the fox guard the henhouse."

The Federal Trade Commission (FTC) stated that the provision could make collusion easier and increase prescription drug prices if a pharmacy board obtains and discloses PBM competitively sensitive information to pharmaceutical manufacturers, pharmacists, and pharmacies.

Mississippi oversees PBMs

The state of Mississippi defends its decision to move PBM oversight to its state board of pharmacy by contending that the new relationship enables the board to regulate licensing and ensure that appropriate statutes are passed—rather than meddle in PBM business.

"We have been aware of the argument against board oversight since it began, but it doesn't hold water," said Steve Parker, PBM administrator for the Mississippi Board of Pharmacy. "We have not overstepped our bounds, we have not said anything against PBMs, and we have not fined them for any of their actions. The board charges a $500 licensure fee, which some PBMs say will cause an increase in prices.

"We are not out for blood," Parker said.

However, he is concerned that transparency regarding PBMs does not exist and that payers have little idea of a PBM's pricing spread.

"Our primary goal is to find out who the PBMs are that operate in our state and how to contact them," Parker said. "Prior to moving oversight to our board, if an issue arose with a PBM in relation to a pharmacy, the only avenue of recourse was through a call center, a toll-free number. Now we are

Continued on pg. 41

ART-related diarrhea

Positively in Control

As unique as ART-related diarrhea is to HIV patients, so is its treatment. With its novel mechanism of action, Fulyzaq™ is the only treatment proven effective for the relief of ART-related diarrhea.[1]

In clinical studies, the most common adverse reactions were upper respiratory tract infection, bronchitis, cough, flatulence, and increased bilirubin.

Diarrhea relief with a distinction

Fulyzaq™
(crofelemer) 125 MG DELAYED-RELEASE TABLETS

Indication

FULYZAQ™ is an antidiarrheal indicated for the symptomatic relief of noninfectious diarrhea in adult patients with HIV/AIDS on antiretroviral therapy.

Important Safety Information about FULYZAQ

FULYZAQ™ (crofelemer) delayed-release tablets should not be used for the treatment of infectious diarrhea. Rule out infectious etiologies of diarrhea before starting FULYZAQ. If infectious etiologies are not considered, and FULYZAQ is initiated based on a presumptive diagnosis of noninfectious diarrhea, then there is a risk that patients with infectious etiologies will not receive the appropriate treatments, and their disease may worsen.

Based on animal data, FULYZAQ may cause fetal harm. Safety and effectiveness of FULYZAQ have not been established in patients less than 18 years of age.

In clinical studies, the most common adverse reactions (occurring in ≥3% of patients and at a rate greater than placebo) were upper respiratory tract infection, bronchitis, cough, flatulence, and increased bilirubin.

Please see brief summary for FULYZAQ [FUHL-ih-zack] on the adjacent page and complete Prescribing Information at **www.Fulyzaq.com**.

Reference: 1. Fulyzaq [prescribing information]. Raleigh, NC: Salix Pharmaceuticals, Inc; 2013.

FUL 13/17

Fulyzaq™

(crofelemer) 125 MG DELAYED-RELEASE TABLETS

The following is a brief summary only; see full Prescribing Information for complete product information at www.Fulyzaq.com.

INDICATIONS AND USAGE

FULYZAQ is an anti-diarrheal indicated for the symptomatic relief of non-infectious diarrhea in adult patients with HIV/AIDS on antiretroviral therapy.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Risks of Treatment in Patients with Infectious Diarrhea

If infectious etiologies are not considered, and FULYZAQ is initiated based on a presumptive diagnosis of non-infectious diarrhea, then there is a risk that patients with infectious etiologies will not receive the appropriate treatments, and their disease may worsen.

Before starting FULYZAQ, rule out infectious etiologies of diarrhea. FULYZAQ is not indicated for the treatment of infectious diarrhea.

ADVERSE REACTIONS

Clinical Trials Experience

A total of 696 HIV-positive patients in three placebo-controlled trials received FULYZAQ for a mean duration of 78 days.

Adverse reactions for FULYZAQ that occurred in at least 2% of patients and at a higher incidence than placebo are provided in Table 1.

Table 1: Adverse Reactions Occurring in at Least 2% of Patients in the 125 mg Twice Daily Group

Adverse Reaction	Crofelemer 125 mg BID* N = 229 n (%)	Placebo BID* N = 274 n (%)
Upper respiratory tract infection	13 (5.7)	4 (1.5)
Bronchitis	9 (3.9)	0
Cough	8 (3.5)	3 (1.1)
Flatulence	7 (3.1)	3 (1.1)
Increased bilirubin	7 (3.1)	3 (1.1)
Nausea	6 (2.6)	4 (1.5)
Back pain	6 (2.6)	4 (1.5)
Arthralgia	6 (2.6)	0
Urinary tract infection	5 (2.2)	2 (0.7)
Nasopharyngitis	5 (2.2)	2 (0.7)
Musculoskeletal pain	5 (2.2)	1 (0.4)
Hemorrhoids	5 (2.2)	0
Giardiasis	5 (2.2)	0
Anxiety	5 (2.2)	1 (0.4)
Increased alanine aminotransferase	5 (2.2)	3 (1.1)
Abdominal distension	5 (2.2)	1 (0.4)

*Twice daily

Adverse reactions that occurred in between 1% and 2% of patients taking a 250 mg daily dose of FULYZAQ were abdominal pain, acne, increased aspartate aminotransferase, increased conjugated bilirubin, increased unconjugated blood bilirubin, constipation, depression, dermatitis, dizziness, dry mouth, dyspepsia, gastroenteritis, herpes zoster, nephrolithiasis, pain in extremity, pollakiuria, procedural pain, seasonal allergy, sinusitis and decreased white blood cell count.

DRUG INTERACTIONS

Drug Interaction Potential

In vitro studies have shown that crofelemer has the potential to inhibit cytochrome P450 isoenzyme 3A and transporters MRP2 and OATP1A2 at concentrations expected in the gut. Due to the minimal absorption of crofelemer, it is unlikely to inhibit cytochrome P450 isoenzymes 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1 and CYP3A4 systemically *[see Clinical Pharmacology (12.3)]*.

Nelfinavir, Zidovudine, and Lamivudine

FULYZAQ administration did not have a clinically relevant interaction with nelfinavir, zidovudine, or lamivudine in a drug-drug interaction trial.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C

Reproduction studies performed with crofelemer in rats at oral doses up to 177 times the recommended daily human dose of 4.2 mg/kg revealed no evidence of impaired fertility or harm to the fetus. In pregnant rabbits, crofelemer at an oral dose of about 96 times the recommended daily human dose of 4.2 mg/kg, caused abortions and resorptions of fetuses. However, it is not clear whether these effects are related to the maternal toxicity observed. A pre- and postnatal development study performed with crofelemer in rats at oral doses of up to 177 times the recommended daily human dose of 4.2 mg/kg revealed no evidence of adverse pre- and postnatal effects in offspring. There are, however, no adequate, well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether crofelemer is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from FULYZAQ, 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.

Pediatric Use

The safety and effectiveness of FULYZAQ have not been established in pediatric patients less than 18 years of age.

Geriatric Use

Clinical studies with crofelemer did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger patients.

Use in Patients with Low CD4 Counts and High Viral Loads

No dose modifications are recommended with respect to CD4 cell count and HIV viral load, based on the findings in subgroups of patients defined by CD4 cell count and HIV viral load.

The safety profile of crofelemer was similar in patients with baseline CD4 cell count less than 404 cells/μL (lower limit of normal range) (N=388) and patients with baseline CD4 cell counts greater than or equal to 404 cells/μL (N=289).

The safety profile of crofelemer was similar in patients with baseline HIV viral loads less than 400 copies/mL (N = 412) and patients with baseline HIV viral loads greater than or equal to 400 copies/mL (N = 278).

Rx Only

Manufactured by Patheon, Inc. for

Salix® Pharmaceuticals, Inc.
Advancing Treatment in Gastroenterology™

Salix Pharmaceuticals, Inc., Raleigh, NC 27615

US Patent Nos. 7,341,744 and 7,323,195.
VENART-267-1 03/13
70027241
FUL 13/20

FULYZAQ is distributed by Salix Pharmaceuticals, Inc. under license from Napo Pharmaceuticals, Inc.

napo pharmaceuticals

The botanical drug substance of FULYZAQ is extracted from *Croton lechleri* (the botanical raw material) that is harvested from the wild in South America.

Should state pharmacy boards regulate PBMs?

Continued from pg. 38

able to resolve 85% to 90% of problems." He emphasized that protecting the consumer is one of the board's key initiatives.

Oklahoma considers oversight

Other states, including Oklahoma, Oregon, and Hawaii, are considering legislation similar to that adopted by Mississippi, allowing pharmacy board oversight.

"Departments of insurance don't have the expertise or ability to oversee PBMs. They don't know what a PBM is," said Oklahoma State Representative David Derby (R-Owasso), who is also a pharmacist, and introduced HB 2100 to bring PBMs under the guidance of the state's board of pharmacy. "The pharmacy board could ensure that PBMs follow regulations. The job of the board should be to protect the public from pharmacists."

Oklahoma's legislation explicitly allows the board of pharmacy to demand confidential information about the business practices of PBMs. The bill has passed in the Oklahoma House but not yet in the state Senate. It will not come up for reconsideration until the legislature meets in 2014.

Derby said that the board of pharmacy would assume the same responsibilities as the insurance department does, monitoring the use of mislabeled drugs, inaccurate dispensing, and expired medications, and would serve as the point of contact for any consumer issues related to PBM activities. A toll-free number is currently the only vehicle. He notes that a PBM's concern over sharing its client information if the board oversees its action is overblown.

"Sensitive materials like contracts are not open to the public," he said.

He, however, admits that as a pharmacist himself, he would like to know about the financial arrangements that PBMs have with drug manufacturers and how much they reimburse pharmacies for dispensing.

"We have been aware of the argument against board oversight since it began, but it doesn't hold water. We have not overstepped our bounds, we have not said anything against PBMs, and we have not fined them for any of their actions."

–Steve Parker, PBM administrator for the Mississippi Board of Pharmacy

NCPA backs oversight

Matthew DiLoreto, director, state government affairs for the National Community Pharmacists Association (NCPA), agrees with Rep. Derby that the switch of oversight to a state board of pharmacy has been blown out of proportion. NCPA says it is imperative that state boards of pharmacy provide oversight to ensure that decisions are made based on the best interests of the patient—a recurring theme among state board proponents.

He said that state boards of pharmacy are the logical place for regulating PBMs, which control more lives than pharmacies, have access to electronic health records, and operate as plans. "If there is any accusation of higher costs, it has to do with the PBM, not with legislation," he said.

While PBMs question the role of the boards in their regulation—citing higher healthcare costs, disclosure of competitive information, and a conflict of interest for pharmacists—NCPA notes that most state legislative proposals that would require PBM licensure by boards of pharmacy also contain provisions that would require both the board of pharmacy and health plan sponsors to treat any information disclosed to it by PBMs as strictly confidential, as it does with pharmacies and pharmaceutical wholesalers.

"Whether it be a PBM or any other entity or individual regulated by a state board of pharmacy, any conflict of interest must be identified and addressed," said Carmen Catizone, executive director, National Association of Boards of Pharmacy.

"PBMs, in terms of their regulation by state boards of pharmacy, should be responsible for the same objective and patient protection processes and goals as any other entity or individual regulated by a state board of pharmacy," Catizone said.

Dismissing any conflict of interest, Catizone said boards must not engage in any actions that involve economic or turf protection objectives. He noted that there would be no more of a conflict of interest than if there were a health-system pharmacist on a board regulating chain or other retail entities that may be competitors—something that he said must be monitored.

In short, Catizone said that state boards should be responsible for the self-regulation of the competency and behavior of pharmacists, as well as ensuring that they are legally accountable and responsible for their practices.

"Similarly, if a PBM is engaged in the practice of pharmacy, it should be regulated by the board of pharmacy fairly, objectively, and competently," he said. DT

Mari Edlin *is a healthcare writer based in Sonoma, Calif.*

Up front
In Depth

Mark Lowery, Content Editor

Tennessee pharmacy board strengthens compounding rules

Less than a month after FDA warned of an outbreak following steroid injections from a compounding pharmacy there, the Tennessee Board of Pharmacy (TBOP) strengthened its oversight of compounding pharmacies.

Under newly adopted rules, the officer of the TBOP, its executive director, and the TBOP commissioner can now jointly suspend a sterile compounder's license for cause without a meeting of the full board.

"The board is working cooperatively to identify solutions to improve safeguards for public health while not placing unnecessary barriers on sterile compounding pharmacies that would hamper production of much-needed drugs already in short supply," said Charles E. "Buddy" Stephens, DPh, TBOP president. "We believe our actions enhance existing safeguards and offer new steps to ensure safe and effective medications are there when needed."

On May 24, FDA reported that 7 Tennesseans had fallen ill after receiving compounded steroid injections made by Main Street Family Pharmacy of Newbern, Tenn. The patients suffered adverse reactions after receiving injections of preservative-free methylprednisolone acetate (80 mg/mL).

Same drug implicated

FDA also advised healthcare providers not to use any products from Main Street Family Pharmacy that were labeled sterile, and to quarantine the products until further notice. The same steroid was involved in the 2012 New England Compounding Center (NECC) fungal meningitis outbreak that killed 58 people and sickened more than 700 others.

In the NECC case, investigators found greenish-yellow residue on sterilized equipment, work surfaces coated with mold and bacteria, and an air conditioner that was supposed to be used to control temperatures shut off at night. FDA investigators also found black foreign matter on 83 of the 321 vials linked to the meningitis outbreak.

FDA confirms bacteria

In the Main Street Family Pharmacy case, FDA found bacteria and fungus in drug vials manufactured by the compounder. It also reported that rooms at the pharmacy that were supposed to be sterile were not, and that basic hygiene procedures were not being followed. Additionally, spiders were found in a clean room.

During inspections in 2011 and 2012, Main Street had been cited for violations that included using outdated medications, prescriptions not written on tamper-resistant paper, and for emailing and dispensing prescriptions without signatures.

TBOP's new rules increase oversight and regulation of Tennessee drug manufacturing operations, with licensed manufacturers now placed into a separate license category. The new regulations require the state's drug manufacturers to show proof that their operations are registered with FDA.

And TBOP has added a sterile compounding registration to the regular pharmacy license, to the manufacturer license, and to the wholesaler/distributor license.

"It's a great challenge to strike a thoughtful, protective balance between addressing the daily drug shortages faced by patients and healthcare providers across Tennessee with the absolute need to assure safety and effectiveness in the compounded product," said John Dreyzehner, MD, MPH, commissioner of the Tennessee Department of Health (TDH). "While we wish the current situation associated with a Tennessee pharmacy had not happened and that patients had not been affected, the actions taken by the board, along with legislation passed recently, are moving us forward in assuring the safety and availability of important medications."

Proactive inspections

TBOP, along with TDH, is reviewing several other regulation changes. TBOP hopes to create a more proactive inspection posture, with additional emphasis on critical reviews of maintenance and quality control records; interim self-assessment and applicable reporting by facilities; and adoption of applicable U.S. Pharmacopeia Standards.

To facilitate the regulation changes, TBOP will hire 3 licensed pharmacists to serve as additional inspectors, and an administrative staffer to assist with the new self-assessment and reporting responsibilities.

"The prior regulatory process resulted in the business ceasing sterile compounding of methylprednisolone acetate almost 2 months before cases were identified," said TDH Chief Medical Officer David Reagan, MD, PhD. "Of course, we never want any patients to be adversely impacted. The actions by the board will strengthen a regulatory system, allowing earlier identification of potential problems." DT

Julia Talsma, Content Channel Director

Customized targeted messaging builds patient loyalty

Have you started offering medication therapy management (MTM) sessions for your chronic disease patients? Are you struggling recruiting or scheduling these patients? Or do you need help with the follow-up to ensure that your patients are doing all that they can to achieve better outcomes?

For independent pharmacists who want to build their pharmacy practices, Prescribe Wellness, a company serving healthcare professionals through marketing, technology, and healthcare expertise, is offering a software service platform designed to help pharmacists complete these tasks.

By creating more efficient and multichannel communication between pharmacists and patients, Prescribe Wellness' software can also help pharmacists target patients who could benefit from services such as smoking cessation.

"With the changes in the Affordable Care Act, the need for preventive care services has never been greater," said Al Babbington, Prescribe Wellness' CEO. "We believe that independent retail pharmacists are in the perfect position to fill in all of these wellness types of services, whether it be diabetic services, smoking cessation, MTM. But they may be struggling with getting the message out to the appropriate patients."

Leveraging pharmacist's voice

Using an automated digital intervention and their own voice, pharmacists can deliver targeted messages to patients. Prescribe Wellness works with pharmacies to identify appropriate patients for specific services such as a diabetes clinic, then creates scripts that detail the steps patients can take to achieve better outcomes. Pharmacists are able to record the messages using their own voices.

"The thing that differentiates our service from the old IVR systems is what we are leveraging—the voice of authority," Babbington said.

Continued on pg. 70

GETTY IMAGES/SCIEPRO/SCIENCE PHOTO LIBRARY

Ben Culpepper, PharmD; David D. Pope, PharmD, CDE; P. Brandon Bookstaver, PharmD

Tackling HIV

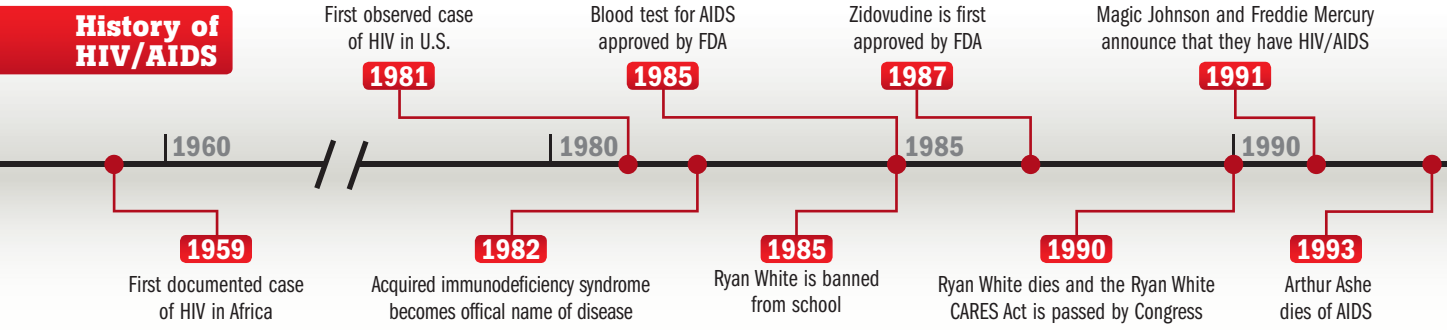
Pharmacists take on screening, treatment

Approximately 1.2 million people in the United States are living with human immunodeficiency virus (HIV), according to the Centers for Disease Control and Prevention (CDC). Of these, 18% are unaware of their HIV status — and are responsible for 50% of all new cases of the disease.

Over the next 20 years, another 1.2 million new HIV infections are estimated to occur, with a lifetime cost of $450 trillion. The current rate of disease progression is simply unsustainable.

Of the individuals who are aware of their HIV status, only half remain in care, meaning that they see their healthcare providers and receive antiretroviral (ARV) agents when indicated. In 2011, there were approximately 32,000 new diagnoses of acquired immunodeficiency syndrome (AIDS) in the United States, according to CDC. (*http://www.cdc.gov/hiv/statistics/basics/index.html*)

History of HIV/AIDS



A SPECIAL SUPPLEMENT

Prepare your health system for handling follow-on biologics 13s

Drug Topics®
VOL. 157 NO. 7
Voice of the Pharmacist
DrugTopics.com
July 2013

READY FOR BIOSIMILARS?

Approval pathway has yet to be tested

PAGE 2s

ADVANSTAR
MEDICAL COMMUNICATIONS GROUP

Teva Cares

Teva U.S. Generics, a division of Teva Pharmaceuticals, brings safe and effective generic medicines to the world in an affordable fashion. We have a long and unparalleled generics heritage—over 100 years to be exact. We're also responsible for one in six prescriptions in the U.S.,* so we understand patients' wants and needs. Our commitment is demonstrated through our strong values hinged on trust, respect, and collaboration. Whether you're a patient, a provider, or a trade partner—*you* matter a great deal to us, and we care about making quality healthcare accessible to you.

You Matter. **We** Care.

For more information on Teva and our line of high quality, affordable generics, please visit ***TevaGenerics.com****.*

TEVA U.S. Generics

*Generic prescriptions. IMS Health NPA data on file at Teva.

Pharmaceuticals

Teva Pharmaceuticals

Teva Pharmaceutical Industries Ltd. is a fully-integrated global pharmaceutical company, focusing its business in three primary areas: generic, specialty, and over-the-counter medicines. Approximately 51% of the company's revenue is generated in the U.S.

Teva's Levalbuterol Inhalation Solution, USP, AN rated to Xopenex® (levalbuterol HCl) Inhalation Solution

Teva recently introduced generic versions of Maxalt® (rizatriptan benzoate) Tablets

Teva Pharmaceuticals is the leading generic drug company in the U.S. In 2012, Teva accounted for 16.2% of U.S. generic prescriptions, with one out of every six* generic prescriptions being filled with a Teva product. The company's strategy for its generic business is to continue to extract maximum value from Paragraph IV patent challenge opportunities; establish a leadership position in high-value generics by pursuing first-to-market opportunities and by developing complex generic products; and to enhance the value of its portfolio by concentrating on high-margin, low competition markets.

Teva has 144 ANDAs pending FDA approval as of April 18, 2013, and introduced 23 generic products in 2012. The company markets the broadest product line in the industry with nearly 400 generic products and 1,300 dosage strengths and package sizes, covering all major therapeutic categories. Teva also produces approximately 300 APIs in many therapeutic areas.

Teva's strategy also includes a disciplined and focused approach to enhancing its specialty branded portfolio, concentrating on the therapeutic areas of CNS, respiratory, oncology, and women's health. Teva's specialty portfolio includes COPAXONE®, AZILECT®, NUVIGIL®, ProAir® and TREANDA®. As part of this strategy, Teva is focusing on new therapeutic entities (NTEs), which are known molecules that are formulated, delivered, or used in a novel way to address specific patient needs.

Teva's Recent Generic Product Introductions	Brand Equivalent
Topotecan Injection	Topotecan Injection
Levalbuterol Inhalation Solution, USP	Xopenex® Inhalation Solution
Olanzapine and Fluoxetine Capsules, USP, 3 mg/25 mg	Symbyax® Capsules
Oxymorphone HCl Tablets	Opana® Tablets
Rizatriptan Benzoate Tablets	Maxalt® Tablets
Carbamazepine Extended-Release Capsules	Carbatrol® Extended-Release Capsules
Tiagabine HCl Tablets (authorized generic)	GABITRIL® (tiagabine hydrochloride) Tablets
Fenofibrate Tablets (authorized generic)	TriCor® (fenofibrate) Tablets
Quinine Sulfate Capsules, USP	Qualaquin® Capsules

** IMS Health NPA data as of 12/2012*

Mari Edlin

Progress report: U.S. development of a biosimilar pathway

Taking as a model the 1984 Drug Price Competition and Patent Term Restoration Act (the Hatch-Waxman Act), which established a generic pathway for small-molecule drugs, the Biologics Price Competition and Innovation Act of 2009 (BPCI) builds on its provisions to meet contemporary technological advances in the development of drugs.

The result gives FDA the power to approve the registration of follow-on biological products that are similar to and in some cases interchangeable with products already approved for sale.

Application guidelines

As prescribed by BCPI, the application for a biosimilar must follow these guidelines:

- Be highly similar to the reference product without clinically meaningful differences in safety, purity, and potency
- Prove biosimilarity using data from analytical studies, animal studies, and clinical studies that are sufficient to demonstrate safety, purity, and potency in one or more appropriate conditions for use for which the reference product is licensed and intended to be used
- Employ the same biological mechanism(s) of action as those of the innovator product
- Indicate the conditions(s) of use prescribed, recommended, or suggested in the proposed product labeling
- Include proof that the biosimilar drug has the same route of administration, dosage form, and strength as that of the innovator product
- Provide information showing that the facility where the biological product is manufactured, packed, or stored meets the same safety standards as the original product

Despite the support of the Affordable Care Act in 2010 and subsequent tweaking of pathway guidelines last year, a process that added three draft guidance document, biosimilars have yet to make use of the abbreviated licensure pathway and place a product in the U.S. marketplace.

In its guidance, FDA recommends that applicants provide a risk-based, "totality of the evidence" approach to support a demonstration of biosimilarity. Applicants are also counseled to use a stepwise approach in their development of biosimilar products.

The numbers

IMS Health has reported that by 2015, sales of biosimilars are

COVER AND THIS PAGE: GETTY IMAGES/ADAM GAULT/OJO IMAGES

expected to reach between $1.9 billion and $2.6 billion, up from $378 million in the first half of 2011.

In a study that highlighted 11 widely used biologics, Express Scripts estimated that with the use of biosimilar products, the United States could save $250 billion over the course of 10 years.

While the difference in price between traditional brands and their generic versions may be as high as 90%, many payers believe total savings from the use of biosimilars would be 10% to 30%, less than the initial estimation of 30% to 40%, according to survey results from Xcenda, a managed market consultancy for biotechnology based in Charlotte, N.C.

Barriers to a pathway

The advantage of the biosimilar pathway is that it requires only an abbreviated approval process that would be shorter than the process designed for a biologics licensing application (BLA) — the route chosen by Teva to market its version of Amgen's Neupogen (filgrastim), for example — but more rigorous than that required of a small-molecule generic.

The follow-on biologic manufacturer has the benefit of piggybacking onto research generated for the patent of the innovator drug, saving the expense and time of duplicating trials already conducted.

Issues and questions

Despite a shorter approval route, the burgeoning industry is running into a few roadblocks, which include lack of clear guidelines; confusion over the assessment of interchangeability, which in turn affects drug substitution; and the naming of the new drugs.

According to Molly Burich, assistant director, reimbursement strategy and health policy for Xcenda, it is unclear whether an established biosimilar pathway should come before or after manufacturers apply for the drug's approval, because no biosimilars have reached the market yet.

"There are several top-selling biologics coming off patent in the next few years, providing an opportunity for biosimilars in the U.S. marketplace, but we have yet to see whether biosimilars can prove to be as safe and effective as their branded counterparts," Burich said.

She added, "After a biologic approval, post-marketing data will be important to assess the impact of biosimilar products."

Guideline goals

Samuele Butera, vice president and head of biopharmaceuticals, Sandoz North America, supports the flexibility of the draft guidance and expects that FDA will provide similar science-based, pragmatic approaches in its final guidelines.

"Limited access to high-quality biologics due to cost of treatment constitutes an unmet medical need in the United States and elsewhere," he said.

"The key is how the FDA will interpret and implement these guidelines, especially around clinical trial requirements," Butera continued. "It is important to recognize that the goal of a biosimilar trial is to prove similarity to the originator and not confirm safety and efficacy all over again."

Sandoz is targeting biosimilars for monoclonal antibodies that treat cancer and autoimmune disorders. The company is focusing on four molecules in six Phase 3 clinical trials.

Interchangeability

At Amgen, a biotechnology company based in Thousand Oaks, Calif., Gino Grampp, executive director of regulatory affairs, affirmed that "Amgen has long supported a biosimilar pathway in the United States and Europe."

He expressed satisfaction with FDA's clear guidance and consistent pathway for moving biosimilars through the pipeline. However, he said, FDA has not yet clearly created a process for determining interchangeability — an important consideration, since patients often switch drugs based on personal effectiveness.

"Europe has laid out the science, and the FDA has engaged in discussions with manufacturers who represent many drugs covering a spectrum of disease states, including 11 reference products, on how to implement a pathway," he said.

With its experience in developing drugs for cancer and rheumatoid arthritis, Amgen plans to bring six biosimilars to market — four oncology drugs and versions of two rivals to the autoimmune agent Enbrel. Its cancer biosimilars will challenge Roche's cancer drugs Avastin, Herceptin, and Rituxan, and Eli Lilly's Erbitux.

According to Grampp, the company plans to produce biosimilars in order to provide new therapeutic options, rather than out of concern about competition for its branded drugs.

"The goal of a biosimilar trial is to prove similarity to the originator and not confirm safety and efficacy all over again."

— Samuele Butera, vice president Sandoz North America

Continued on pg. 8s

LUPIN
PHARMACEUTICALS, INC.

BUILT TO GROW—Lupin has now recorded 8 consecutive years of strong growth, making them the 14th largest generic pharmaceutical company in the world by revenue. Lupin is dedicated to delivering high-quality branded and generic medications, trusted by healthcare professionals and patients across the U.S. Lupin is the 5th largest generic manufacturer in the U.S. (by prescriptions) and one of the fastest growing generic pharmaceutical companies in the U.S. This continuous growth can be attributed to a strong pipeline, solid customer relationships, and flawless execution.

SUSTAINED GROWTH—Lupin's sustained growth in revenue stems from a culmination of entities. They have forged a unique growth strategy for the Advanced Markets built around quality niche products, world-class research, manufacturing, and supply chain capabilities. Lupin recognizes the importance of R&D and has invested 7.5% of its FY 2012 net sales in this area. In FY 2013, the U.S. Generics business reported growth of 52% with revenues of $548 million USD, up from $361 million USD in FY 2012.**(unaudited figures)*

SUPPLY CHAIN—As the demands of the U.S. generic pharmaceutical market continue to grow, so does Lupin. Lupin have expanded their manufacturing capabilities over the past several years with additional state-of-the art facilities to exceed customer demands and strengthen their overall supply chain by creating efficiencies that ensure a cutting edge response time, thus creating unrivaled value. Lupin has earned its reputation as a global pharmaceutical company on the back of consistent and reliable delivery of high-quality products. Lupin's customers trust them to act responsibly and deliver safe and effective medications at affordable costs.

BY THE NUMBERS

- **58 total generic products**
- **Launched 13 generic products in FY 2013**
- **FY 2013 Revenue of $548 million USD**

API—Lupin's global formulations business is built on the backbone of one of the most efficient API businesses in the world. Lupin is one of the most vertically integrated global generic companies and remains the leader in therapeutic areas such as Cephalosporins, Cardiovasculars, and anti-TB products.

THE LUPIN FLOWER— The company was named after the Lupin flower because of the inherent qualities of the flower and what it personifies and stands for. The Lupin flower is known to nourish the land; the very soil it grows in. The Lupin flower is also known to be tolerant of infertile soils and capable of pioneering change in barren and poor climates.

THE FUTURE—Lupin is a fully integrated pharmaceutical company with a major global presence. This presence was built on its platforms of cutting-edge research, world-class manufacturing facilities, and a truly global supply chain. With these building blocks in place, the future looks even brighter.

www.lupinpharmaceuticals.com

Recent Generic Launches	Brand Equivalent
Fenofibrate Tablets	TriCor®
Valsartan & Hydroclorothiazide Tablets USP	Diovan HCT®
Irbesartan & Hydrochlorothiazide Tablets USP	Avalide®
Levonorgestrel and Ethinyl Estradiol Tablets USP	Lutera®
Daysee™ (Levonorgestrel & Ethinyl Estradiol Tablets USP)	Seasonique®

Lupin – expanding relationships built on trust with our ***new*** oral contraceptive line of products

Trust is at the core of our pharmaceutical business

You already know Lupin Pharmaceuticals, Inc. as one of the leading suppliers of high-quality generic pharmaceutical products. We have launched a variety of oral contraceptives and are committed to growing an extensive portfolio of OC's in the future. Call us to find out more about our latest offerings

LUPIN

Enhancing Women's Care™

Call (866) 587-4617 or visit www.birthcontrolhealth.com

OC07012013DT

DR. REDDY'S

Delivering quality and affordability has always been the goal at Dr. Reddy's

Today, more than a decade since the launch of our first finished dosage-form product in North America, we continue to find ways to bring value to the pharmacy and meet the demands of a changing market.

With investments in product development, aggressive acquisitions, and advances in research, processes, and technologies, we're keeping healthcare costs contained while improving access to medications across the United States.

As part of a global, vertically integrated, pharmaceutical company from India, we have rapidly become one of the leaders in the supply of generic APIs worldwide with four finished-dosage facilities servicing North America.

Through its three businesses, Pharmaceutical Services and Active Ingredients, Global Generics, and Proprietary Products, Dr. Reddy's offers a portfolio of products and services including APIs, custom pharmaceutical services, generics, biosimilars, differentiated formulations, and NCEs. We have capabilities to help overcome market-entry barriers, ranging from formulation issues to intellectual property. What's more, we are uniquely positioned to support Rx-to-OTC switches.

Dr. Reddy's at a Glance:

- Prescription products: 60+ products are marketed under Dr. Reddy's label in 250+ dosing presentations

- OTC products: 11 products are marketed in 200+ store-brand packaging presentations (private label)
- Robust pipeline: 65 ANDAs are pending, of which 38 are Para IV certifications and 8 FTFs
- Dosage forms: Oral solids, injectables, liquids, topicals, and other forms are available
- 33 Rx products ranked top 3 in market share
- Rank 10th of Corporations in TRx dispensed*

*IMS Health, National Prescription Audit, Dec. 2012

DR. REDDY'S

LIFE. RESEARCH. HOPE

Now Available...

The **FIRST** And **Only** Generic **Desloratadine** Orally Disintegrating Tablets, 2.5 mg and 5 mg

- *Generic Equivalent To Clarinex® Reditabs® (desloratadine)*
- *Available In 30 Count*

Reditabs® is a registered trademark of MSD CONSUMER CARE, INC.
Clarinex® is a registered trademark of Merck Sharp & Dohme Corp.

DR. REDDY'S

Dr. Reddy's Laboratories, Inc.
200 Somerset Corporate Blvd., Building II, 7th Floor
Bridgewater, NJ 08807
Tel: 866-733-3952 www.drreddys.com

 RDY-0313-003 February 2013

Progress report: U.S. development of a biosimilar pathway

Continued from pg. 3s

He predicts that 2017 will most likely be the year for the first biosimilar to hit the U.S. marketplace depending on how long studies take to complete and what drugs come off patent. Grampp said, however, that not every biologic is ripe for development of a follow-on drug.

Cost containment

Looking through the lens of a pharmacy benefits manager (PBM), Peter Wickersham, senior vice president, cost of care for Prime Therapeutics based in Eagan, Minn., said that biosimilars are the missing link to keeping the cost of drugs down.

"Overall drug spend rose only 2.7% last year due to generics, which enabled PBMs and plans to construct programs around their use. We need the new pathway in order to be actionable and functional."

While the determination of interchangeability is an FDA responsibility, it is up to individual states to assess drug substitution of biosimilars for originator drugs.

Patent expirations

FDA has granted reference drugs a 12-year exclusivity period, during which the follow-on biologic manufacturer cannot refer to the data submitted by the innovator in its original application for FDA approval. Two federal budget proposals request a modification, limiting exclusivity to seven years.

While some industry experts believe that patent exclusivity might delay the arrival of biosimilars, Everett Neville, vice president, chief trade relations officer for Express Scripts, a pharmacy benefits manager based in St. Louis, said that originator drugs should have a period of patent protection. Of greater concern to Express Scripts are the patents that are set to expire in the next few years.

"Once these patents expire, these therapies would be likely candidates for biosimilars. At that point, the primary obstacle that may delay biosimilar manufacturers from bringing these more affordable products to market within the United States would be uncertainty about the approval process for biosimilars," Neville said.

BPCI calls for a four-year waiting period between the date of the innovator's license application and that of the follow-on biologic. Once the biosimilar hits the marketplace, it will receive a one-year exclusivity period.

More than 40 biologics will face patent expiration between 2013 and 2020, worth $65 billion in sales, according to Covance, a biopharmaceutical development services company.

Drug substitution

While BPCI clearly notes the importance of interchangeabiity between biologics and their follow-on counterparts, the issue of substituting the new drugs at the pharmacy level is not written in stone.

It is difficult to determine interchangeability and whether substitution is warranted, said Xcenda's Burich — especially since patients can react differently to the same drug.

"If there isn't interchangeability, substitution of a biosimilar will not be automatic — at least not initially," she said.

Grampp said that his company supports safe substitution of biosimilars if the drugs are interchangeable, if patients are included in the discussion, and if pharmacists communicate with physicians after the fact, rather than concurrently.

"We are surprised by the 'notification provision,' which offers a real disadvantage," he said. "We are concerned with accurate clinical results at the patient level, and if a drug loses effectiveness, we can look at patients' electronic health records to see what they are taking."

State inaction

While the determination of interchangeability is an FDA responsibility, it is up to individual states to assess drug substitution of biosimilars for originator drugs.

According to Phil Katz, co-head of the pharmaceutical and biotech regulatory practice group at Hogan Lovells in Washington, D.C., manufacturers are trying to lobby for legislation that would hamper prescription of biosimilars, while also making it difficult for biosimilar developers to study the original product.

Three states — North Dakota, Virginia, and Utah — have passed legislation making it more difficult to allow substitutions of biosimilars, while four states have rejected regulations and eight others are discussing the issue.

Many opponents of such legislation say it is premature, discouraging the use of biosimilars before approval has even occurred. On the other hand, some drug manufacturers are pushing for physician authority to specify "Do not substitute."

Unlike North Dakota's legislation, laws passed by Virginia, the first state to take action, and Utah contain a two-year sunset clause pertaining to physician notification and record-keeping requirements; however, the clauses are expected to be denied before biosimilars even come to market.

Continued on pg. 12s

NOW AVAILABLE from **MYLAN**®

2013**GBR**®
Generic Brand Reference

How do we demonstrate our commitment to pharmacy professionals every day?

See inside.

We provide educational resources, like the *GBR*®—*Generic Brand Reference*—Guide, to pharmacists and pharmacy technicians. The 2013 *GBR* Guide, which contains a comprehensive, cross-referenced listing of generic and brand pharmaceuticals, is now available in print and as an app for Apple®* devices. In mid-2013, it will also be available for Android™† and BlackBerry®‡ smartphones.

To order the FREE print edition, go to Mylanpharms.com. To download the FREE app, scan the code at right for Apple devices, or go to the appropriate app store, search for "Mylan *GBR* Guide," and follow the instructions.

Discover how Mylan supports you with high quality medicine and resources.

Mylanpharms.com

**Registered trademark of Apple, Inc.*
†Trademark of Google Inc.
‡Registered trademark of Research in Motion (RIM).

Mylan®
Seeing is believing

Boehringer Ingelheim
Roxane Laboratories

A Connection to Excellence

For your patients and for patients everywhere who rely on our products

Behind every Roxane product, you'll find a team that connects you to the people who work tirelessly to bring economical generic pharmaceuticals to patients everywhere. With continual advances in cutting-edge administration and dosage for more than 100 medications, and ongoing efforts to keep our product line affordable and available to as many customers as possible — the team at Roxane Laboratories is laser focused on meeting and exceeding the needs of each and every one of our customers and patients.

Roxane Laboratories operates as the research and development and sales and marketing arms of Boehringer Ingelheim's multisource pharmaceutical business. Today, Roxane markets more than 100 medications in 300 package sizes.

We are committed to expand our line of multisource pharmaceutical products that are formatted as bulk and unit-dose package configurations for liquids and solids; coated, sustain-released and controlled-release tablets; nasal sprays; topical solutions; cytotoxics; and CII narcotics.

Advancements in controlled substances, sustain-released items, potent compounds, unit doses, and bulk packaging all reflect our dedication to provide customers with innovative, technically complex products from our FDA-approved facilities.

The team at Roxane understands how every aspect of our business can affect your patients' lives— everything from answered phones calls to correct shipments and efficient manufacturing processes. We strive for excellence with every customer experience and are committed to provide quality products for a range of clinical areas.

Roxane also recognizes that growth and development in our product lines impact patients everywhere. Our team contains highly skilled researchers who are constantly working to expand the number of our generic pharmaceuticals. These scientists, combined with our patent-experienced attorneys and purchasing team, are tasked with putting more affordable generic treatments on the market and into your hands—as soon as possible.

Our award-winning pursuit of high-quality products and service is also accompanied by a lean manufacturing model staffed by a skilled, flexible workforce. This innovative manufacturing and business practice allows for quick shifts in production based on marketing opportunities and business needs. As always, Roxane maintains impressive levels of safety, quality, and compliance.

To meet the changing needs of our patients, Roxane has continued to grow our product lines to offer a variety of treatment options. To accommodate this growth, we expanded our Wilson Road facility in Central Ohio by adding a 105,000-square-foot complex in 2011. Like all our efficient operations, this facility meets the rigorous design standards required for safe and compliant manufacturing.

Quality, safe, and affordable growth has continued for Roxane in 2012. We are proud to have launched these eleven new generic products:

- **Dipyridamole Tablets, USP**
- **Quetiapine Fumarate Tablets**
- **Tinidazole Tablets**
- **Hydromorphone Hydrochloride Oral Solution, USP**
- **Nevirapine Tablets**
- **Nevirapine Oral Suspension**
- **Montelukast Sodium Tablets**
- **Montelukast Sodium Chewable Tablets**
- **Oxcarbazepine Oral Suspension**
- **Irbesartan and Hydrochlorothiazide Tablets, USP**
- **Irebesartan Tablets, USP**

Key Executives:

Randy Wilson, General Manager

Paul Kersten, R.Ph., Vice President, Sales and Marketing

Mark Boudreau, Executive Director of Sales

Michael Plessinger, Director of Marketing

Visit roxane.com to view our complete product catalog and reach our TouchPoint Customer Service Center 24/7 for information about your account and order status.

Roxane. Right Now™

Roxane Laboratories

Your Connection to Excellence™

Answered phone calls. Correct shipments. Efficient manufacturing processes. Forward-thinking research. Roxane Laboratories is working to bring generic pharmaceuticals to our customers, to people everywhere who depend on our products. With continual advances in cutting-edge administration, dosage for more than 100 medications and ongoing efforts to develop economical pharmaceuticals—Roxane is your connection to quality, growth, affordability and innovation.

Roxane. Right Now.™

QUALITY	GROWTH	AFFORDABLITY	INNOVATION

roxane.com

Progress report: U.S. development of a biosimilar pathway

Continued from pg. 8s

"Lawmakers in Virginia carefully considered this legislation and made several important changes before it was enacted," said Jonah Houts, vice president, state government affairs, Express Scripts. He believes that the sunset clause allows legislators to evaluate whether any inadvertent barriers to patient or prescriber use of interchangeable biosimilars are included.

The Virginia law enables the prescribing physician to forbid the substitution of a biosimilar; requires that FDA declare the biosimilar "interchangeable"; and mandates that a pharmacist must notify the prescriber of a substitution within five days of dispensing, as well as inform the patient of the retail cost of both the innovator medication and the biosimilar substitution.

It also requires pharmacists and prescribers to keep records of the substitution for two years, for reference in case an adverse event should arise.

The legislation in Utah is similar to the law that passed in Virginia.

According to Butera, Sandoz is concerned that ongoing state-level lobbying efforts by originator companies could have a negative impact on the ability of pharmacists to help drive the successful introduction of affordable, high-quality biosimilars in the United States.

"These efforts are aimed at introducing additional, unnecessary, and scientifically unjustified hurdles at the physician, pharmacy, and individual patient," he said.

Naming conventions

Because biosimilars are not identical to their innovator counterparts, FDA may require that biosimilars and their reference biologics be named differently, in which case it will be necessary to create a new International Nonproprietary Name (INN) for follow-on drugs, unlike the protocol the World Health Organization (WHO) has prescribed for small-molecule generics.

Christopher Topoleski, director of federal regulatory affairs at the American Society of Health-System Pharmacists (ASHP), outlined the varying positions on the naming of biosimilars:

- They should share the same generic name as that of the brand
- Every biosimilar should have a unique name, different from that of the innovator biologic
- There should be a compromise that uses the generic name of the innovator product, but with either a suffix or a prefix to differentiate it from the innovator

Because biosimilars are not identical to their innovator counterparts, FDA may require that biosimilars and their reference biologics be named differently.

"There should be nothing inherent in the naming of a product that would hinder approval, but different generic names would be a different situation, in terms of substitution, from what prescribers and patients are used to, in terms of their past experience with generic drugs," he said. "On the other hand, exactly the same name could create challenges for accurate post-marketing surveillance."

To Butera, the push to create distinct names for biosimilars does not make sense scientifically. "If drug manufacturers succeed in their efforts, they will slow appropriate substitution of interchangeable biosimilars, threaten patient access, and prevent patients and payers from realizing substantial savings in years to come," he said.

On the other hand, Amgen, maker of Enbrel for rheumatoid arthritis, supports the WHO policy for biologics, agreeing that distinguishable names will enable international regulators, healthcare providers, and patients to easily identify biosimilars, thus reducing the chance of inappropriate and inadvertent product-switching.

"It is important to recognize the manufacturer of a biosimilar if an adverse effect occurs," said Grampp.

He added, "It is a different story for small-molecule generics, because usually, if there is a problem, it reflects a problem with an entire class of drugs rather than with a specific product. If nonproprietary names are used, it will be impossible to figure out who the manufacturer is."

Lessons from Europe

"Europe is clearly ahead of the United States in implementing a biosimilar pathway," Butera said. "It not only introduced a legislative framework for biosimilar approval from 2004 onward, but it also has approved a total of 14 biosimilars over the past seven years."

Sandoz introduced Omnitrope (a growth hormone) in Europe in 2006, later approved in the United States through a new drug application the same year. It was followed by two other biosimilars, Binocrit (for treatment of anemia associated with chronic renal failure) and Zarzio (to increase production of white blood cells), which have not yet received U.S. approval.

"While there are certainly a number of factors to account for the current differences between Europe and the United States, including different patent expiry dates for some products, we believe the strength of originator lobbying campaigns here has played a key role," Butera said. DT

Mari Edlin *is a healthcare writer in Sonoma, California.*

Fred Gebhart, Contributing Editor

Preparing for biosimilars

The first wave of biologic agents was greeted with celebration and consternation when they entered the market in the 1980s and 1990s. Celebration, because agents such as human growth hormone, alpha interferon, tissue plasminogen activator, and erythropoietin offered new hope and new treatments for intractable diseases. Consternation, because no one, including pharmacy professionals, had any experience dealing with this new class of agents.

Biologics aren't drugs, yet they are managed like drugs at the pharmacy, hospital, and health-system levels. They devoured frighteningly large chunks of limited pharmacy budgets. Both their therapeutic and side-effect profiles were riddled with question marks, in part because no one, including manufacturers, had the technology to fully characterize their structure, composition, or method of action.


James Stevenson

Fast-forward to 2013. The Patient Protection and Affordable Care Act (ACA) has created a pathway for the approval of follow-on biologics. The prospect of therapeutic equivalents to some of the most effective and most expensive therapeutics now available is sending similar waves of celebration and concern through the current generation of pharmacy managers, pharmacy and therapeutics committees, and health-system budget managers. There is celebration over the prospect of competition, therapeutic alternatives, and lower prices. The consternation arises over the prospect of yet another new category of therapeutic agents with unclear characterization, uncertain therapeutic interchangeability, and unknown fiscal impact.

Or maybe not. Pharmacy, P&T committees, and budget managers have decades of experience dealing with biologic agents, both on and off patent. They just don't realize it.

Lessons of the past

Take insulin, for example. It was the first biologic agent to be approved by the Food and Drug Administration in the distant era of 1982. Most of the commonly used insulins today are biologics, said James Stevenson, PharmD, director of pharmacy services at the University of Michigan Health System as well as dean and professor in clinical sciences at the University of Michigan College of Pharmacy in Ann Arbor, Mich.

Or consider erythropoietin (EPO), first approved in 1989. Multiple versions of EPO are in clinical use and deciding which version to use is a non-issue for most health systems.

"The same principles that guide substitutions and switches between Novolog [insulin aspart (rDNA origin), Novo Nordisk] and Humalog [insulin lispro (rDNA origin), Lilly] or between Epogen [epoetin alfa, Amgen] and Aranesp [darbepoetin alfa, Amgen] apply to other biologics as well," Stevenson told *Drug Topics*.

"Novolog and Humalog are not identical, but therapeutically, they are very similar. Most health systems don't carry both, just one of them. We have learned how to interchange them. Those lessons don't change just because we are looking at $23 billion worth of biologics coming off patent between now and 2019."

What does change is what happens to biologics when they go off patent and another manufacturer attempts to enter the market. When small-molecule drugs lose patent protection, the market is quickly flooded with generic equivalents.

Generics sometimes enter the market as soon as patents on the reference product expire; sometimes the innovator brand and the generic competitor cut a deal to allow earlier competition. Sometimes there are extended court battles as the innovator tries to maintain patent protection and revenue streams; sometimes the transition comes without objection. But regardless of the precise sequence of events for any particular product, everyone from innovator to P&T committee, pharmacy, prescriber, patient, payer, and generic manufacturer knows that prices will plummet. As multiple suppliers enter the marketplace, generic pricing typically falls to somewhere between 40% and 10% of the patent-protected product.

Continued on pg. 16s

Hi-Tech Pharmacal: A Solid Source of Quality

With over three decades of experience serving retail and institutional pharmacy, this publicly traded (Nasdaq:HITK) American company prides itself on its longstanding commitment to exemplary service and its innovative line of prescription, OTC, and specialty products.

David Seltzer, president and CEO, commented, "We are very pleased with our performance in the first half of 2013 – particularly in our ability to drive sales while still making significant increases in our commitment to important long-term strategic initiatives like research and development, manufacturing and supply chain integration, and a continual improvement in customer service and support."

Hi-Tech has the expertise necessary to develop and manufacture liquid and semi-solid dosage forms, nasal sprays – such as Fluticasone Propionate, generic for Flonase® – and products that require sterile manufacturing.

Hi-Tech currently has 15 products pending FDA approval, including partnered products, and approximately 20 products in various stages of development. These products represent approximately $6.3 billion in branded sales, and include dosage forms ranging from oral liquids to ophthalmics. This is consistent with the company's mission to continually expand its range of products, dosage forms, and packaging configurations.

Additionally, Hi-Tech is now well established in the development of its Unit Dose program, with four offerings currently on the market, and four more planned for introduction in the next nine months.

To support such an ambitious and dynamic pipeline, Hi-Tech maintains an ongoing program of growing its R&D efforts. This year alone, the company has increased its expenditures in research and development by over 50 percent in the fiscal year ended April 30, 2013. The company has increased spending on internal projects for the generic division, which include five projects that require clinical trials. Clinical trials for two of these projects are currently ongoing.

Successful launches have included Levofloxacin Ophthalmic Solution, Gabapentin Oral Solution (under 180-day exclusivity), Lidocaine Jelly 2%, Ranitidine Syrup, Levetiracetam Oral Concentrate, and Levofloxacin Oral Solution (also under 180-day exclusivity). Levofloxacin Oral Solution is the generic for Levaquin®.

Hi-Tech's branded subsidiary, ECR, offers a broad range of products indicated for the treatment of allergies, headaches, and dermatitis/poison ivy. This effort is supported with a growing sales force of full-time field representatives. Current brands include DexPak®, Bupap®, Tussi-Caps®, Orbivan®, Zolpimist®, and Zolvit®.

Additionally, Hi-Tech Pharmacal offers a range of well-known OTC brands like Zostrix® through its subsidiary HCP. HCP's primary focus is on the fast-growing diabetes specialty market, with offerings such as Diabetic Tussin® and Diabeti-Derm®.

"We're committed to finding ways to deliver value at Hi-Tech," Seltzer said. "We're driven by the same core values we established when the company was founded in 1981 — focus, innovation, confidence, and trust."

Seltzer exhibits the confidence that comes with success. "We remain very optimistic about our future," he said. "We see tremendous opportunity ahead of us as our generics pipeline is more robust than ever."

Ed Berrios, Hi-Tech vice president of sales and marketing, added, "One of the most important things we can do for our customers is to continue to grow our portfolio of key and niche products. Adding new dosage forms and technical capabilities, developing new products – everything we do is about helping our customers help their patients."

"We understand that the pharmacies aren't just our customers, they're our partners in business," Berrios said. "We make sure that their success and satisfaction is always at the top of our business goals."

For more information, visit **www.hitechpharm.com.**

Product lines change. Values remain.

As one of the generic industry's most experienced manufacturers of liquid, semi-solid, and specialty generic pharmaceuticals, Hi-Tech Pharmacal has earned the trust of pharmacists across the country. For more than three decades, we have combined innovation and a keen sense of the market to continually deliver important new products and capabilities — including a sterile production facility and a range of unique dosage forms. And while our rapidly expanding product line continues to provide new opportunities for our pharmacy and distribution partners, one thing remains the same — our unwavering commitment to quality, service and innovation. To learn more about our products and business solutions, visit **hitechpharm.com** or contact us at **800.262.9010**.

Scan for more information.
To download a barcode reader,
please visit getreader.com on your mobile device.

Hi·Tech PHARMACAL Co. Inc.

Preparing for biosimilars

Continued from pg. 13s

POTENTIAL BIOSIMILARS IN THE UNITED STATES

Product	Brand name	Manufacturer	FDA approval	Potential market entry	2012 U.S. sales (billions)
Filgrastim	Neupogen	Amgen	1991	2013	$0.96
Etanercept	Enbrel	Immunex	1998	2014	$4.04
Epoetin alfa	Epogen/Procrit	Amgen	1989	2014	$3.14
Infliximab	Remicade	Centocor/Janssen Biotech	1998	2014	$3.72
Trastuzumab	Herceptin	Genentech	1998	2014	$1.79
Rituximab	Rituxan	Genentech	1997	2015	$3.13
Pegfilgrastim	Neulasta	Amgen	2002	2015	$3.32
Adalimumab	Humira	AbbVie	2002	2019	$4.33
Bevacizumab	Avastin	Genentech	2004	2019	$2.56
Darbepoetin alfa	Aranesp	Amgen	2001	2019	$0.88

Sources: Food & Drug Administration, Drugs.com

Biosimilar, not bioequivalent

The future isn't so simple for biologics. For starters, there is no such thing as a generic biologic product. There never will be, Stevenson said, because of the nature of biologics.

Small-molecule pharmaceuticals are synthetic compounds that can be created almost anywhere by anyone who has the recipe, the raw materials, the equipment, and the know-how to put them all together in a formulation that meets FDA requirements. Atorvastatin is the same molecule whether it carries the Lipitor (Pfizer) brand name or is made by Apotex, Dr. Reddys, Kudco Ireland, Mylan, Ranbaxy, Sandoz, or another generic manufacturer.

"You can't create an exact copy of biologics," Stevenson said. "These large molecules are grown through biologic processes, not created by synthetic chemistry. The best you can hope for is to create another large molecule that is biologically similar and therapeutically equivalent to the original agent. There is no such thing as bioequivalence for large molecules. But there can be biosimilarity."

Part of the problem is legal and historical. Drugs are regulated by the Food, Drug, and Cosmetic Act (FDCA, passed in 1938). Most biologics are regulated under the Public Health Service Act (PHSA, 1944), although a small number of biologics, including insulin, some hormones, and a few enzymes, falls under FDCA because they were already on the market when PHSA was passed.

Regulatory authority matters, said Stevenson, because generic drugs have their roots in the Hatch-Waxman Act, formally known as the Drug Price Competition and Patent Term Restoration Act, passed in 1984. The bill created two pathways for FDA approvals of generic equivalents of reference-drug products approved under the FDCA. Generic manufacturers could seek approval with an Abbreviated New Drug Application under section 505(j) of Hatch-Waxman for products that contained the same active ingredient as the reference product. Most generics are approved with an ANDA.

The second pathway, section 505(b)(2), allows approval for generics that are not identical to the reference product, but are similar in action. This pathway has been used to approve generic versions of human insulin and Omnitrope (somatropin [rDNA origin], Sandoz), some of the few generic biologics on the market in the United States.

Outside the handful of biologics that fall under FDCA, there has not been a regulatory approval process for a follow-on product. The Generic Pharmaceutical Association pushed FDA to approve biologics under the existing framework in 2002, but the Biotechnology Industry Organization filed a Citizen's Petition in 2003 that effectively blocked approvals of follow-on biologic agents.

Rx benefit implications

Pressure for approval of follow-on biologics continued. In 2006, the European Commission approved Omnitrope, the world's first successor to an innovator biologic. The European Medicines Agency, the European Union equivalent of the FDA, dubbed Omnitrope a biosimilar, a term that's been adopted worldwide.

In the United States, attention focused on the cost of biologics. A year of Avastin (bevacizumab, Genentech) for breast cancer costs about $92,000, Stevenson noted. A year of Cerezyme (imiglucerase, Genzyme) costs about $200,000. In 2006, Medicare alone spent $2.8 billion for Epogen, more than the entire $1.863 billion FDA budget for that fiscal year. In 2007, Express Scripts estimated cost savings of more than $71 billion over 10 years from just the first four classes of biologics expected to face biosimilar competition: interferons, erythropoietins, growth hormones, and insulin.

"There will be significant pressure from all sides to utilize biosimilars to

control healthcare costs," Stevenson said. "There will be significant financial pressure to consolidate market share around a product. Payers will be exerting pressure, clinicians will be exerting pressure, patients will be exerting pressure, manufacturers will be exerting pressure. Pharmacy is in the middle, trying to navigate all these conflicting pressures."

Balancing the conflicting pressures to use one product rather than another is as much a technical problem as it is a clinical conundrum, he continued. Current information technology systems are designed to work with generic products that are, at least in theory, freely interchangeable. There is no need to distinguish one generic from another for clinical purposes. Few health systems track which patient received which product and which formulation from which manufacturer; they simply track the product and formulation.

That level of product identification may be appropriate for generics, Stevenson said, but not for biosimilars. The key concept is "similar."

Practical implications

Biosimilar does not mean not bioidentical. Biosimilars can be expected to have slightly different pharmacokinetic and pharmcodynamic characteristics compared to the reference product and compared to each other. Side-effect profiles may be different. Because each biosimilar is a unique molecule, each may have unique therapeutic and immunogenic effects.

"We need to track precisely which product each patient was exposed to," Stevenson said. "This level of tracking is crucial for pharmacovigilance and post-marketing studies. We need to identify precisely which agent a patient received."

The FDA has standard naming conventions for most therapeutics, he continued, but not for biosimilars. Until and unless the agency develops and then enforces naming conventions, health systems may have to devise their own tracking systems to identify different biosimilars.

The one thing that is unlikely to change is how health plans evaluate and reimburse biosimilars. Health plans recognize that each biosimilar is a unique therapeutic entity. Expect protocols to evaluate biosimilars that look very much like those that are currently used to evaluate new brand-name products and formulary reviews.

Once plans decide where to place a new biosimilar on formulary, expect to see all the usual patient incentives employed to drive biosimilar use. Tiered coverage, differential copays, and other familiar tools will all come into play.

The challenge, Stevenson said, is to determine the level of studies and clinical data needed to establish therapeutic equivalence between biosimilars and reference products. If two products, either a biosimilar and its reference product or two biosimilars, are considered therapeutically equivalent, the next question is how — or whether — to cover one, all, or none?

Transitions of care are a similar challenge. How do pharmacists deal with patients who enter a hospital or health system on biosimilar A, when the system formulary mandates biosimilar B? The same question could emerge at discharge, when the patient may be on biosimilar B and the outpatient formulary mandates another biosimilar or the reference agent.

"The therapeutic equivalence principles we all know and use every day need to be applied to biosimilars," he said. "We need to think about how, or whether, we will do a therapeutic interchange program for each biosimilar."

Pharmacy implications

Biosimilars are not likely to arrive tomorrow, or even next year, Stevenson said. That gives pharmacy time to consider options and create effective programs to appropriately manage biosimilars.

But there is not much time. As FDA is still finalizing the details of biosimilar approval processes, drugmakers are preparing their own biosimilar submission programs. The first biosimilars could become available as early as 2015, but there are at least eight biologics with sales of $1 billion or more with patents that expire between 2013 and 2019.

"What pharmacists can do now is educate themselves about biologics and biosimilars, and how they are different from the small molecules we know from years of experience," Stevenson said. "Biologics are a very fast-growing expense category. That is why payers are so eager to get biosimilars into the mix."

But just as large-molecule biologics are more complex and more expensive than small-molecule drugs, biosimilars will be more expensive than generics. Generic savings can reach 90% of reference-product prices. The savings from biosimilars are more likely to fall in the range of 30% of the cost of reference brands.

"That translates into a very substantial sum, but it is not the kind of savings we are accustomed to with generics," Stevenson cautioned. "Biosimilars will reduce the rate of growth in spending. Drug spending will continue to grow, but at a somewhat lower rate. We can expect to see utilization tools such as prior authorization and significant copays or coinsurance to encourage the use of biosimilars."

He concluded, "It is time to work with P&T committees on strategies to deal with biosimilars and ways to handle hand-offs when patients enter and leave the system. These are things that need to be discussed in detail over the next year or so. But these are not discussions that are foreign to us. We have done all of this before with new biologics and new therapeutic agents." DT

Contributing Editor **Fred Gebhart** *works all over the world as a freelance writer and editor, but his home base is in Oregon.*

amneal®
PHARMACEUTICALS

Outstanding Products and Service for Pharmacists and Their Patients

Amneal Pharmaceuticals, LLC is an award-winning American manufacturer with an unwavering commitment to delivering exceptional quality generic medications and outstanding customer service to both pharmacists and their patients. Amneal is driven by a strong sense of family values, utmost integrity, superior operational execution, and dedication to building true customer partnerships that create value. The company is the 7th largest U.S. generics supplier based on number of prescriptions dispensed, according to March 2013 IMS Health data.

Broad Product Selection

With 61 ANDAs filed and another 129 in development, the Amneal product portfolio is well-positioned for growth. Amneal offers over 250 products across multiple therapeutic categories including central nervous system, pain, cardiovascular, oncology, opioid dependency treatment, urology, dermatology, women's health, and diabetes. Medications range from mainstream oral solids to complex controlled substances, hormonal products, and high potency formulations. The company continues to diversify its product mix by adding new therapeutic areas and dosage forms such as injectables, transdermal patches, creams, and ointments.

Earlier this year, Amneal launched several new products, including a first-to-market generic for Suboxone® (buprenorphine and naloxone) tablets (CIII). Other products new to Amneal's catalog include Sildenafil Citrate (AB-rated to Revatio®), Warfarin Sodium (AB-rated to Coumadin®), Potassium Chloride Extended Release, and Metaxalone Tablets (AB-rated to Skelaxin®). Several first-to-file and first-to-market launches are planned along with exciting new dosage forms as well as vertically integrating products using Amneal's own API.

Rich Online Catalog Resource

Extensive information on all Amneal products can be found in the online product catalog at amneal.com. This comprehensive resource is designed for easy access to in-depth product information such as product specifications, inactive ingredients, and allergens. Also posted on the product detail page are high-resolution images, labels, full prescribing information, patient medication guides, material safety data sheets (MSDS), and HDMA sheets. With a few clicks, pharmacists and patients can locate the exact resources and answers they need.

A Passion for Customers

In recognition of Amneal's strong industry reputation for providing the highest quality generic medicines and superb service levels at a fair price, the firm has received major industry awards for achievement of excellence across all facets of its operations.

According to its customers, the company consistently provides outstanding service, fast response to inquiries or problems, top-quality products, and reliability of supply. Employees listen closely to customers and implement product formulation changes and innovative packaging improvements based on their feedback. Amneal believes that a firm commitment to keeping its small-business values – to doing business the right way – is the true path to achieving both customer and corporate success.

No Matter How Far We've Come, Our Course Remains True.

The introduction of our latest generic is another example of how we've remained steadfastly focused on quality, integrity and the pharmacist-patient relationship.

New Release: Generic equivalent to

Suboxone®

(buprenorphine and naloxone) Tablets (CIII)

As Amneal progresses along its incredible journey, we continue to stay focused on the values and principles that led us through such tremendous growth. Whether it's the release of a new first-to-market generic, a new pharmacist-defined label, innovative packaging improvements, additional dosage forms or new therapeutic categories, we're still Amneal to the core. Our commitment to quality, integrity, and the value of the pharmacist-patient relationship will not waiver.

That's what makes Amneal...Generic's New Generation.

amneal® PHARMACEUTICALS

Suboxone® is a registered trademark of Reckitt Benckiser Group plc.
Product shown is not actual size

Generic's New Generation **amneal.com**

Camber Pharmaceuticals Shows Continued Growth as It Focuses on Customer Satisfaction in the Generic Marketplace

As an organization, the goal of Camber Pharmaceuticals Inc. is to be its customer's first choice for multisource generic prescription products. Camber strives to be the most reliable and cost-effective generic pharmaceutical supplier across a broad range of therapeutic classes. Camber manufactures and markets a superior value to the generic marketplace. From quality API's, intermediates, finished goods to exceptional customer service and logistics, the Camber story has become a standard of excellence in the pharmaceutical industry.

Camber's product line continues to grow

With new product releases that include *Indomethacin ER, Indomethacin, Gabapentin Tablets and Capsules, Levocetirizine, Levetiracetam, Levetiracetam Oral Solution, Escitalopram Oral Solution and Escitalopram Tablets*, Camber will remain one of the fastest growing generic companies in the USA for years to come. Camber has been recognized as one of the top 20 overall pharmaceuticals companies in Dispensed Prescriptions. Cambers commitment to the consumer is to bring the highest quality generic pharmaceuticals to the market to improve quality of life through cost-effective medications.

"Camber Cares" — Camber continues its charitable efforts

Working with highly respected non-profits such as AmeriCares, Blusource, Project Hope, and Brothers Brother, demonstrates the value Camber places on giving back to the community. Through these organizations, Camber's products have reached over 40 countries around the world, helping provide various prescription drugs from anti-hypertensive to antiretroviral medications. Camber is not only proud to provide resources that will assist the needs of many people, but views strategic donations as a responsibility to society. Camber is committed to providing donations in the future and is currently expanding their partnerships with charitable organizations.

Increasing Capacity is Key to Camber's Future

Camber is a wholly owned subsidiary of Hetero Drugs based in Hyderabad, India. **Hetero Drugs** is a global pharmaceutical, research and development company with emphasis on API production and the manufacture of finished dosage forms and currently markets over 200 products and has a robust pipeline.

Camber is in the early stages of adding an additional 300,000 sq. ft. of warehouse and distribution space near its current facility in Piscataway N.J. Camber's associate company and manufacturing partner, **Invagen Pharmaceuticals, Inc.**, located in Hauppauge, N.Y., has recently added a 250,000 sq. ft. manufacturing facility, greatly increasing its capacity and bringing its total space to 375,000 sq. ft. Invagen focuses on a wide range of therapeutic areas including, cardiovascular, anti-infective, CNS, anti-inflammatory, anti-diabetic and antidepressants. This combination of proficiencies gives Camber the unique ability to control every aspect of the manufacturing process, from API to finished dosage. With an impressive list of additional products scheduled for 2012, Camber is poised to become one of the largest generic pharmaceutical suppliers in the U.S.

Camber Pharmaceuticals Inc.
Established 2007
Contact: KON OSTAFICIUK, President
Sales Headquarters Address: 1031 Centennial Ave Piscataway, NJ. 08854
Phone: (732) 529-0430
Fax: (732) 562-8788
Web site: www.camberpharma.com

Making a world of difference in generics...

one dose at a time.

Helping today's pharmacists meet the challenges of the future with quality generics.

CAMBER PHARMACEUTICALS, INC. Phone: 732.529.0430 • CamberPharma.com

CAMBER™ PHARMACEUTICALS, INC.

NOW AVAILABLE from **MYLAN**®

2013**GBR**®
Generic Brand Reference

How do we demonstrate our commitment to pharmacy professionals every day?

See inside.

We provide educational resources, like the *GBR*®—*Generic Brand Reference*—Guide, to pharmacists and pharmacy technicians. The 2013 *GBR* Guide, which contains a comprehensive, cross-referenced listing of generic and brand pharmaceuticals, is now available in print and as an app for Apple®* devices. In mid-2013, it will also be available for Android™† and BlackBerry®‡ smartphones.

To order the FREE print edition, go to Mylanpharms.com. To download the FREE app, scan the code at right for Apple devices, or go to the appropriate app store, search for "Mylan *GBR* Guide," and follow the instructions.

Discover how Mylan supports you with high quality medicine and resources.

Mylanpharms.com

**Registered trademark of Apple, Inc.*
†Trademark of Google Inc.
‡Registered trademark of Research in Motion (RIM).

Mylan®
Seeing is believing

Learning curve

The management of HIV/AIDS has seen unparalleled progress in a relatively brief time. In approximately 30 years, our knowledge of the disease and development of treatment options have transformed a diagnosis of HIV from a terminal disease with a short life expectancy to a chronic disease with sustainable long-term management. Yet despite the investment in research and development, and despite the tremendous strides that have been made, only 1 out of every 4 persons living with HIV achieves the goal of viral suppression – or undetectable viral load (HIV RNA) in the blood.

As we continue to progress in our management of the disease, pharmacists have the opportunity to help alleviate the burden associated with HIV. Pharmacists, especially those practicing in the community, can be valuable members of interdisciplinary teams; they can assist in identifying the estimated 236,400 patients unaware of their status, linking them to specialty care, reducing the likelihood of medication errors, and ensuring medication adherence, thus having a positive effect on patients' $CD4^+$ cell counts and level of viremia.

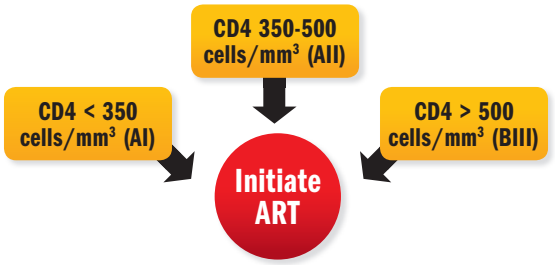
History

Relatively speaking, HIV is a fairly young disease. Although unconfirmed, it is assumed that the most common HIV strains made the jump from chimpanzees to humans sometime in the late 19th or early 20th century.

One of the more common theories connected with its origin is the "Hunter Theory," which suggests transmission through zoonosis, the transmission of an infection from an animal to a human. In this case, chimpanzees infected with simian immunodeficiency virus (SIV) transmitted the virus when a hunter was bitten or cut, exposing the hunter to SIV, which mutated into HIV. The virus is thought to have made its way to the United States by way of Haiti sometime in the late 1960s or early 1970s.

In 1981, the CDC published a report detailing accounts of 5 previously healthy homosexual males in their late 20s to mid-30s, presenting with *Pneumocystis carinii* pneumonia (PCP, now *Pneumocystis jiroveci*) in the Los Angeles area. Although it could not have been known at the time, this report marked the beginning of the HIV/AIDS epidemic in the United States.

Figure 1. Initiation of antiretroviral therapy



According to Department of Health and Human Services guidelines, initation of antiretroviral therapy (ART) should be considered once a patient's $CD4^+$ cell count reaches a certain point. An "A" rating signifies a strong recommendation, and a "B" rating signifies a moderate recommendation. The I-III ratings signify the level of evidence behind those recommendations, with I being the most rigorous.

Source: http://aidsinfo.nih.gov/guidelines

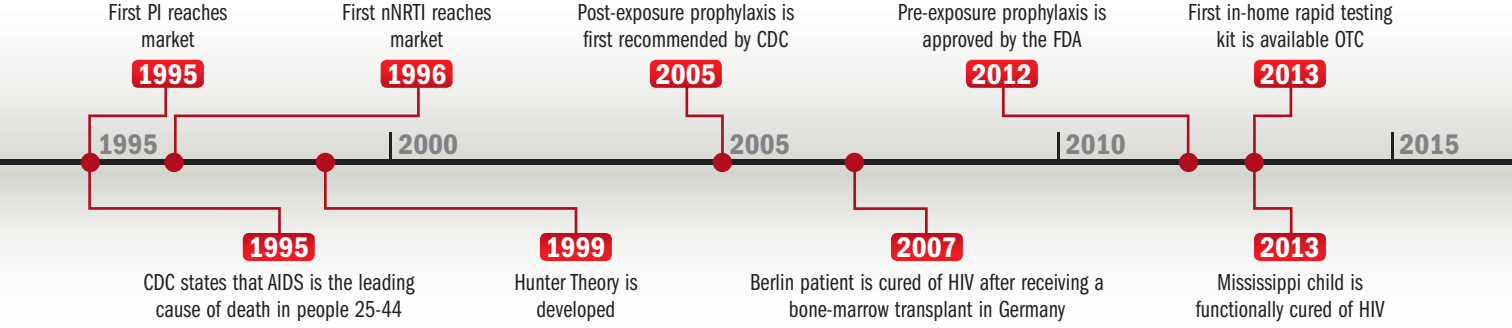
In September 1982, the CDC officially coined the term "acquired immunodeficiency syndrome (AIDS)." (The timeline accompanying this article indicates other major events in the history of HIV/AIDS.)

No treatment options were available until March 1987, when zidovudine (Retrovir), a nucleoside reverse transcriptase inhibitor (NRTI), became the first ARV agent to win FDA approval. The NRTIs were the only drug class available until ritonavir (Norvir) and indinavir (Crixivan), the first protease inhibitors (PI), were approved in March 1996.

After approval of the PIs, delavirdine (Rescriptor), the first non-nucleoside reverse transcriptase inhibitor (nNRTI), received FDA approval in April 1997. In 2003, the first fusion inhibitor was approved, followed by the CCR5 antagonists and integrase inhibitors (InSTI) in 2007. With the approval of Stribild last year, which includes elvitegravir (a novel InSTI) with a pharmacokinetic enhancer and two NRTIs, there are 24 different ARV agents, among six different drug classes, currently approved and available for the treatment of HIV.

Screening

Approximately 236,000 individuals unknowingly living with HIV are responsible for almost 50% of new infections. One



way to reduce the burden of new HIV infections is by identifying those with previously unknown HIV-positive status and linking them to care. It has been well documented that if a patient is receiving therapy, the risk of transmission is decreased. Two organizations offer recommendations on HIV screening: the CDC and the U.S. Preventive Services Task Force (USPSTF).

In the past, their guidelines recommended that patients classified as "high-risk" should be regularly screened. Beginning in 2006, the CDC recommended universal screening of adults <65 years. As of April 2013, both organizations now recommend that everyone between the ages of 15 and 65 years be screened. The availability of these tests has expanded beyond physicians' offices and emergency rooms into community pharmacies and even into in-home testing.

Treatment guidelines

The primary set of treatment guidelines used in the United States was published by the Department of Health and Human Services (DHHS) and endorsed by the CDC. The guideline authors meet on a monthly basis to determine whether updates or amendments to the guidelines are needed.

With the 2012 and 2013 updates, DHHS has made significant changes to its treatment recommendations. Previously, the recommendation was to wait to initiate therapy until patients' CD4 counts fell below 200 cells/mm^3. This recommendation has now changed, as more evidence has shown that earlier initiation has resulted in better patient outcomes and decreased transmission rates. (See Figure 1 for the most recent DHHS recommendations on when to initiate therapy.)

In addition to its recommendations related to CD4 counts, DHHS recommends earlier initiation of antiretroviral therapy (ART) as a step toward decreasing transmission rates. This recommendation is grounded in concern for public health.

Therapy options

Once the decision is made to initiate therapy, the guidelines offer specific treatment options. The DHHS guidelines recommend a potent ARV combination therapy for initial treatment (Figure 2). Generally, a potent ART regimen consists of 2 NRTIs, plus either 1 nNRTI, a ritonavir-boosted PI, or an InSTI (Figure 3).

The patient's lifestyle and desire to initiate medications should be at the center of any treatment-related decisions. HIV/AIDS differs from most chronic disease states, in that there are no proven nonpharmacologic therapies for its treatment. Antiretroviral agents are responsible for the extended life expectancy and decreased transmission rates.

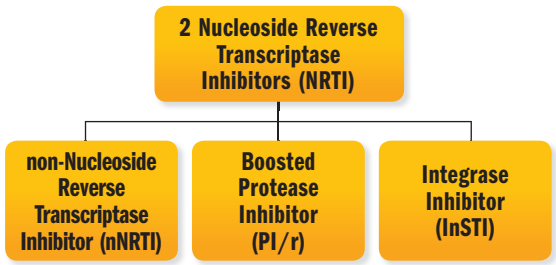
It is imperative that patients taking ARV medications remain adherent. While an adherence rate of 80% is generally acceptable for other disease states such as diabetes or hypertension, this is not the case with HIV/AIDS. Patients must be at least 95% adherent with their ART in order to prevent development of resistance and transmission of the disease, according to a 2000 report published by the *Annals of Internal Medicine* (Paterson DL and colleagues).

There are now combination products such as emtricitabine/tenofovir (Truvada; Gilead Sciences) or lamivudine/zidovudine (Combivir; GlaxoSmithKline) that give patients their NRTI "backbone." In addition, there are 3 full-regimen combination products that come in once-daily single-pill regimens (Stribild, Gilead Sciences; Atripla, Gilead Sciences/Bristol-Myers Squibb; Complera, Gilead Sciences).

Even though the regimens have become simpler and the pill burden has decreased, medication adherence

Continued on pg. 49

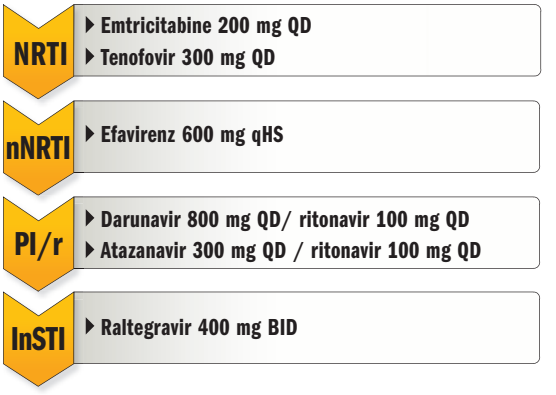
Figure 2. Selection of antiretroviral therapy



When a regimen for a treatment-naïve patient is selected, two agents from the top row and one agent from the second row should be chosen.

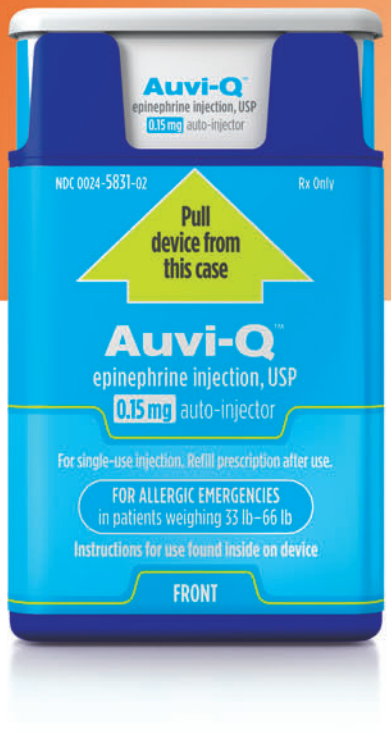
Source: http://aidsinfo.nih.gov/guidelines

Figure 3. Preferred agents for each drug class for ART-naïve patients: 2013 DHHS guidelines



Source: http://aidsinfo.nih.gov/guidelines

What does Auvi-Q offer my patients at risk for anaphylaxis?



I talk.

Auvi-Q is available for adults and children weighing greater than 33 lb. Features include:

- **Audio and Visual Cues** guide users step by step through the injection process
- **Press-and-Hold** injection mechanism with 5-second hold time
- **Retractable Needle** designed to help prevent accidental needle sticks
- **Unique Compact Size and Shape**

Indication
Auvi-Q™ (epinephrine injection, USP) is indicated in the emergency treatment of allergic reactions (Type I) including anaphylaxis to allergens, idiopathic and exercise-induced anaphylaxis. Auvi-Q is intended for individuals with a history of anaphylaxis or who are at risk for anaphylactic reactions.

Important Safety Information
Auvi-Q should **ONLY** be injected into the anterolateral aspect of the thigh. DO NOT INJECT INTO BUTTOCK OR INTRAVENOUSLY.

Epinephrine should be administered with caution to patients with certain heart diseases, and in patients who are on medications that may sensitize the heart to arrhythmias, because it may precipitate or aggravate angina pectoris and produce ventricular arrhythmias. Arrhythmias, including fatal ventricular fibrillation, have been reported in patients with underlying cardiac disease or taking cardiac glycosides or diuretics. Patients with certain medical conditions or who take certain medications for allergies, depression, thyroid disorders, diabetes, and hypertension, may be at greater risk for adverse reactions. Adverse reactions to epinephrine include anxiety, apprehensiveness, restlessness, tremor, weakness, dizziness, sweating, palpitations, pallor, nausea and vomiting, headache, and/or respiratory difficulties.

Auvi-Q is intended for immediate self-administration as emergency supportive therapy only and is not a substitute for immediate medical or hospital care.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

Please see brief summary of Prescribing Information on the next page.

Auvi-Q™
epinephrine injection, USP
0.15 mg/0.3 mg auto-injectors
TALKS YOU THROUGH

Scan this code or go to auvi-q.com/hcp to watch the demo

Watch the demo video and learn more at auvi-q.com/hcp

SANOFI US.EAI.13.02.019 3/13 Printed in U.S.A.

Auvi-Q™ **Rx Only**
(epinephrine injection, USP) 0.3 mg, 0.15 mg Auto-Injector

Brief Summary of Prescribing Information

1 INDICATIONS AND USAGE

Auvi-Q™ is indicated in the emergency treatment of allergic reactions (Type I) including anaphylaxis to stinging insects (e.g., order Hymenoptera, which include bees, wasps, hornets, yellow jackets and fire ants) and biting insects (e.g., triatoma, mosquitoes), allergen immunotherapy, foods, drugs, diagnostic testing substances (e.g., radiocontrast media) and other allergens, as well as idiopathic anaphylaxis or exercise-induced anaphylaxis.

Auvi-Q™ is intended for immediate administration in patients who are determined to be at increased risk for anaphylaxis, including individuals with a history of anaphylactic reactions.

Anaphylactic reactions may occur within minutes after exposure and consist of flushing, apprehension, syncope, tachycardia, thready or unobtainable pulse associated with a fall in blood pressure, convulsions, vomiting, diarrhea and abdominal cramps, involuntary voiding, wheezing, dyspnea due to laryngeal spasm, pruritus, rashes, urticaria or angioedema.

Auvi-Q™ is intended for immediate self-administration as emergency supportive therapy only and is not a substitute for immediate medical care.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 EMERGENCY TREATMENT

Auvi-Q™ is not intended as a substitute for immediate medical care. **In conjunction with the administration of epinephrine, the patient should seek immediate medical or hospital care.** More than two sequential doses of epinephrine should only be administered under direct medical supervision [*see INDICATIONS AND USAGE (1), DOSAGE AND ADMINISTRATION (2) and PATIENT COUNSELING INFORMATION (17.1 in the full prescribing information)*].

5.2 INCORRECT LOCATIONS OF INJECTION

Auvi-Q™ should **ONLY** be injected into the anterolateral aspect of the thigh [*see DOSAGE AND ADMINISTRATION (2) and PATIENT COUNSELING INFORMATION (17.1 in the full prescribing information)*].

- **Do not inject intravenously.** Large doses or accidental intravenous injection of epinephrine may result in cerebral hemorrhage due to sharp rise in blood pressure. Rapidly acting vasodilators can counteract the marked pressor effects of epinephrine if there is such inadvertent administration.
- **Do not inject into buttock.** Injection into the buttock may not provide effective treatment of anaphylaxis. Advise the patient to go immediately to the nearest emergency room for further treatment of anaphylaxis.
- **Do not inject into digits, hands or feet.** Since epinephrine is a strong vasoconstrictor, accidental injection into the digits, hands or feet may result in loss of blood flow to the affected area. Advise the patient to go immediately to the nearest emergency room and to inform the healthcare provider in the emergency room of the location of the accidental injection. Treatment of such inadvertent administration should consist of vasodilation, in addition to further appropriate treatment of anaphylaxis [*see ADVERSE REACTIONS (6)*].

5.3 ALLERGIC REACTIONS ASSOCIATED WITH SULFITE

Epinephrine is the preferred treatment for serious allergic reactions or other emergency situations even though this product contains sodium bisulfite, a sulfite that may, in other products, cause allergic-type reactions including anaphylactic symptoms or life-threatening or less severe asthmatic episodes in certain susceptible persons.

The presence of a sulfite in this product should not deter administration of the drug for treatment of serious allergic or other emergency situations even if the patient is sulfite-sensitive.

The alternatives to using epinephrine in a life-threatening situation may not be satisfactory.

5.4 DISEASE INTERACTIONS

Some patients may be at greater risk for developing adverse reactions after epinephrine administration. Despite these concerns, it should be recognized that the presence of these conditions is not a contraindication to epinephrine administration in an acute, life-threatening situation. Therefore, patients with these conditions, and/or any other person who might be in a position to administer Auvi-Q™ to a patient experiencing anaphylaxis should be carefully instructed in regard to the circumstances under which epinephrine should be used.

- Patients with Heart Disease
  Epinephrine should be administered with caution to patients who have heart disease, including patients with cardiac arrhythmias, coronary artery or organic heart disease, or hypertension. In such patients, or in patients who are on drugs that may sensitize the heart to arrhythmias, epinephrine may precipitate or aggravate angina pectoris as well as produce ventricular arrhythmias [*see DRUG INTERACTIONS (7) and ADVERSE REACTIONS (6)*].
- Other Patients and Diseases
  Epinephrine should be administered with caution to patients with hyperthyroidism, diabetes, elderly individuals, and pregnant women. Patients with Parkinson's disease may notice a temporary worsening of symptoms.

6 ADVERSE REACTIONS

Adverse reactions to epinephrine include anxiety; apprehensiveness; restlessness; tremor; weakness; dizziness; sweating; palpitations; pallor; nausea and vomiting; headache; and/or respiratory difficulties. These symptoms occur in some persons receiving therapeutic doses of epinephrine, but are more likely to occur in patients with hypertension or hyperthyroidism [*see WARNINGS AND PRECAUTIONS (5.4)*].

Arrhythmias, including fatal ventricular fibrillation, have been reported, particularly in patients with underlying cardiac disease or those receiving certain drugs [*see WARNINGS AND PRECAUTIONS (5.4) and DRUG INTERACTIONS (7)*].

Rapid rises in blood pressure have produced cerebral hemorrhage, particularly in elderly patients with cardiovascular disease [*see WARNINGS AND PRECAUTIONS (5.4)*].

Angina may occur in patients with coronary artery disease [*see WARNINGS AND PRECAUTIONS (5.4)*].

Accidental injection into the digits, hands or feet may result in loss of blood flow to the affected area [*see WARNINGS AND PRECAUTIONS (5.2)*].

Adverse events experienced as a result of accidental injections may include increased heart rate, local reactions including injection site pallor, coldness and hypoesthesia or injury at the injection site resulting in bruising, bleeding, discoloration, erythema or skeletal injury.

7 DRUG INTERACTIONS

Patients who receive epinephrine while concomitantly taking cardiac glycosides, diuretics, or anti-arrhythmics should be observed carefully for the development of cardiac arrhythmias [*see WARNINGS AND PRECAUTIONS (5.4)*].

The effects of epinephrine may be potentiated by tricyclic antidepressants, monoamine oxidase inhibitors, levothyroxine sodium, and certain antihistamines, notably chlorpheniramine, tripelennamine, and diphenhydramine.

The cardiostimulating and bronchodilating effects of epinephrine are antagonized by beta-adrenergic blocking drugs, such as propranolol.

The vasoconstricting and hypertensive effects of epinephrine are antagonized by alpha-adrenergic blocking drugs, such as phentolamine.

Ergot alkaloids may also reverse the pressor effects of epinephrine.

8 USE IN SPECIFIC POPULATIONS

8.1 PREGNANCY

Teratogenic Effects: Pregnancy Category C.

There are no adequate and well controlled studies of the acute effect of epinephrine in pregnant women.

Epinephrine was teratogenic in rabbits, mice and hamsters. Epinephrine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus (fetal anoxia, spontaneous abortion, or both).

Epinephrine has been shown to have teratogenic effects when administered subcutaneously in rabbits at approximately 30 times the maximum recommended daily subcutaneous or intramuscular dose (on a mg/m^2 basis at a maternal dose of 1.2 mg/kg/day for two to three days), in mice at approximately 7 times the maximum daily subcutaneous or intramuscular dose (on a mg/m^2 basis at a maternal subcutaneous dose of 1 mg/kg/day for 10 days), and in hamsters at approximately 5 times the maximum recommended daily subcutaneous or intramuscular dose (on a mg/m^2 basis at a maternal subcutaneous dose of 0.5 mg/kg/day for 4 days).

These effects were not seen in mice at approximately 3 times the maximum recommended daily subcutaneous or intramuscular dose (on a mg/m^2 basis at a subcutaneous maternal dose of 0.5 mg/kg/day for 10 days).

8.3 NURSING MOTHERS

It is not known whether epinephrine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Auvi-Q™ is administered to a nursing woman.

8.4 PEDIATRIC USE

Auvi-Q™ may be given safely to pediatric patients at a dosage appropriate to body weight [*see DOSAGE AND ADMINISTRATION (2)*]. However, studies in pediatric patients weighing less than 15 kg (33 pounds) have not been conducted.

8.5 GERIATRIC USE

Clinical studies of Auvi-Q™ 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. Epinephrine should be administered with caution in elderly individuals, who may be at greater risk for developing adverse reactions after epinephrine administration [*see WARNINGS AND PRECAUTIONS (5.4), OVERDOSAGE (10)*].

10 OVERDOSAGE

Overdosage of epinephrine may produce extremely elevated arterial pressure, which may result in cerebrovascular hemorrhage, particularly in elderly patients. Overdosage may also result in pulmonary edema because of peripheral vascular constriction together with cardiac stimulation. Treatment consists of rapidly acting vasodilators or alpha-adrenergic blocking drugs and/or respiratory support.

Epinephrine overdosage can also cause transient bradycardia followed by tachycardia, and these may be accompanied by potentially fatal cardiac arrhythmias. Premature ventricular contractions may appear within one minute after injection and may be followed by multifocal ventricular tachycardia (prefibrillation rhythm). Subsidence of the ventricular effects may be followed by atrial tachycardia and occasionally by atrioventricular block. Treatment of arrhythmias consists of administration of a beta-adrenergic blocking drug such as propranolol.

Overdosage sometimes results in extreme pallor and coldness of the skin, metabolic acidosis, and kidney failure. Suitable corrective measures must be taken in such situations.

Revised September 2012

Manufactured for:
sanofi-aventis U.S. LLC
Bridgewater, NJ 08807

A SANOFI COMPANY

EPI-BPLR-SA-SEP12

Tackling HIV

Continued from pg. 46

should be emphasized and positively reinforced with every patient interaction.

New developments

While the past 20 years have seen major developments in this area of treatment, recently there have been significant breakthroughs, and the foreseeable future is likely to bring more.

In July 2012, emtricitabine /tenofovir (Truvada) was given an additional indication for use in pre-exposure prophylaxis (PrEP). With this new indication, HIV-negative patients will have a pharmacologic option for prevention of virus transmission from a sero-positive partner.

The introduction of dolutegravir (ViiV Healthcare) will bring a relatively benign adverse effect profile to the market. This could become the preferred agent in that class of medications.

There is ongoing research into NRTI-sparing regimens, which may help decrease long-term side effects.

On the subject of vaccines for prevention of HIV infection, the trials have been relatively disappointing thus far. That is not to say that a vaccine will never happen, but it is further down the line.

The search for a functional cure that would make medication therapy no longer necessary has been energized recently by the cases of the Berlin patient who became virus-neutral following a complete bone-marrow transplant and the baby in Mississippi who achieved similar status after receiving immediate treatment once the infection was discovered. Although their circumstances are different, both of the patients appear to have been functionally cured.

Opportunities for community pharmacy

From decreasing the pill load to preventing serious interactions and strengthening adherence, pharmacists are key influences when it comes to improving the lives of patients and supporting public health.

In addition to the public health benefits, there also is a significant business case to be made for pharmacies to focus on HIV management. HIV medications cost, on average, $2,000 to $5,000 per month and can run as high as $28,000 per month. Patients living with HIV may also spend more on over-the-counter products and complementary therapies; they may also visit the pharmacy more often.

Community pharmacists can take simple measures to attract and assist patients living with disease. One option is to offer in-depth, MTM-style meetings with HIV patients. By providing education along with a medication review, pharmacists may discover underlying issues of nonadherence and prevent medication-related issues in the future.

Another way to attract patients living with HIV is to provide compliance packaging that addresses their complex regimens and comorbid conditions, such as cardiovascular disease and diabetes. In this connection, pharmacists can use packaging systems typically employed by assisted living facilities to improve adherence.

Finally, pharmacists can also implement adherence reporting for physicians who prescribe ART. Pharmacies that have implemented this simple strategy have reported increased numbers of HIV-related prescriptions coming in from satisfied physicians.

VIDEOS

Cleveland Clinic experts – Leonard Calabrese, DO, Vice Chair, Rheumatic and Immunologic Diseases, R.J Farenmyer Center for Clinical Immunology, and Andrea Pallotta, PharmD, BCPS, Clinical Specialist-Infectious Diseases/HIV – spoke with *Drug Topics* about some of the greatest breakthroughs since the introduction of the first antiretroviral agent in 1987 and their collaborative management of newly diagnosed HIV patients. **http://drugtopics.com/HIVmanagement**

How we can help

In relative terms, the understanding and treatment of HIV/AIDS have come a long way over the past 30 years. There is still a long way to go, as treatment shifts from dealing with a terminal illness to managing a chronic disease with multiple comorbidites, such as cardiovascular disease and diabetes.

To help maximize therapeutic benefits, medication experts must be integral members of the team. Pharmacists have a relationship with their patients that other healthcare providers do not, and they are in a position to significantly affect disease-state management. Rated among the most accessible and trusted healthcare professionals, pharmacists have access to the complete medication profile, including OTC medications; they can identify drug-drug interactions or medication errors; and they are aware of the degree to which patients adhere to their medications.

As the stigma of HIV continues to fade, pharmacists will capitalize on the opportunity to serve HIV patients, and in turn, provide a win-win situation for all – the patient, healthcare professionals, and public well being. DT

Ben Culpepper, PharmD, *is the PGY-2 community/academia pharmacy resident with Kerr Drug and the University of North Carolina School of Pharmacy in Chapel Hill, N.C.*

David Pope, PharmD, CDE, *is chief of innovation and co-founder of CreativePharmacist.com.*

P. Brandon Bookstaver, PharmD, *is associate professor, University of South Carolina College of Pharmacy, Columbia, S.C.*

DOSING ISSUES Katie S. Buehler, PharmD, BCPS and Abigail M. Yancey, PharmD, BCPS

Anticoagulant dosing in obesity should be individualized and drug-specific

Obesity is a growing problem in the United States. Currently, 68% of adult Americans are overweight (BMI >25 kg/m^2).[1] Of those, 35% are obese (BMI >30 kg/m^2) and 6% are morbidly obese (BMI >40 kg/m^2).[1-2] It is estimated that by 2030, 51% of the population will be obese and 11% will be morbidly obese.[1] We are often confronted with dosing drugs in an obese patient. Unfortunately, many clinical trials exclude or have limited overweight patients enrolled; thus, optimal dosing for both safety and efficacy in this population is lacking. Pharmacokinetic studies in obese patients have shown that the volumes of distribution of lipophilic drugs and the clearance of hydrophilic drugs can be increased.[3,4] For this reason, dosing in obesity should be patient- and drug-specific.

Unfractionated heparin

Obese patients are often initiated on anticoagulation for venous thromboembolism (VTE) prophylaxis, VTE treatment, or acute coronary syndrome (ACS) treatment. Concerns for bleeding in obese patients have raised the question of whether dose adjustments or dose capping is necessary. Unfractionated heparin (UFH) has a nonlinear pharmacokinetic profile and is not distributed into adipose tissue.[4] Studies have shown that total body weight (TBW) is the most important predictor of anticoagulation requirements.[5–7] However, physicians are often cautious of abnormally high doses of UFH. One retrospective study found that based on recommended dosing guidelines, only 10% of obese patients received the correct bolus dose and only 25% were initiated on the correct infusion dose. The gap between the recommended dose and prescribed dose amplified as body weight increased.[8]

Since the adoption of TBW UFH protocols, numerous studies have been undertaken to determine optimal dosing in obese patients. Multiple studies have supported the use of TBW dosing protocols for obese patients.[9,10] However, some studies found that using TBW, morbidly obese patients required smaller infusion rates or experienced greater aPTT values compared to their controls.[11–14]

Low-molecular-weight heparins

Low-molecular-weight heparins (LMWHs) are predominantly concentrated in the plasma with little distribution into adipose tissue.[15] Guidelines offer little guidance except suggesting anti-Xa monitoring with subsequent dose adjustments in obese patients.[16] Focusing on treatment dosing, some studies have compared anti-Xa levels based on weight in obese and non-obese patients and determined that dose adjustments may not be necessary.[17] Bazinet et al found that when utilizing weight-based dosing of enoxaparin without dose capping there was no difference in subtherapeutic, therapeutic, or supratherapeutic levels among patients treated for atrial fibrillation (AF), ACS, or VTE.[18]

"We are often confronted with dosing drugs in an obese patient. Unfortunately, many clinical trials exclude or have limited overweight patients enrolled; thus, optimal dosing for both safety and efficacy in this population is lacking."

Data from trials have not confirmed increased bleeding in obese patients. Al-Yaseen et al found rates of bleeding with dalteparin to be consistent with those previously reported, without significant alterations in anti-Xa levels.[19] A retrospective review found no difference in the rate of major hemorrhage between obese and non-obese patients with ACS.[20] The Computerized Registry of Patients with Venous Thromboembolism (RIETE) suggested no significant difference in recurrent VTE between obese (>100 kg) and non-obese patients treated with LMWH. Doses may have been capped; therefore, strong conclusions cannot be drawn.[21] Pooled results suggest that to ensure adequate anticoagulation, treatment doses of UFH and LMWH should be based on TBW without capping. Due to conflicting results, special consideration and close monitoring should be taken into account when dosing morbidly obese patients with UFH. Anti-Xa monitoring may be appropriate for obese patients on LMWH therapy especially those weighing >190 kg as data are particularly lacking in these patients.[22]

Continued on pg. 53

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

Anticoagulant dosing in obesity should be individualized

Continued from pg. 50

Concerns also exist with underdosing UFH and LMWH for VTE prophylaxis since obesity itself is a risk factor for the development of VTE in the hospitalized medical patient.[23] Guidelines suggest that obese surgical patients or patients undergoing bariatric surgery may require higher prophylactic doses.[24] Strategies such as increasing the fixed dose or administering a TBW-based dose have been studied. A study looking at morbidly obese patients found that heparin 7,500 units 3 times daily or enoxaparin 40 mg twice daily decreased VTE occurrence by 50% compared to standard prophylactic regimens.[25] A subgroup analysis showed that compared to placebo, fixed-dose dalteparin was equally effective in non-obese and obese patients; however, no benefit was seen in patients with a BMI >40 kg/m^2.[26] Scholten et al compared higher than normal fixed-dosing strategies (enoxaparin 30 mg or 40 mg twice daily) in bariatric surgery patients. Results showed a decrease in VTE utilizing 40 mg twice daily without an increase in major bleeding.[27] A retrospective analysis found that enoxaparin 0.5 mg/kg twice daily was effective at maintaining prophylactic anti-Xa levels without increasing major bleeds.[28] Based on results of clinical trials, standard fixed doses of LMWH and UFH may not provide adequate VTE prophylaxis in obese patients. Trials have demonstrated that various dosing strategies providing higher doses of LMWH and UFH may be necessary.

Warfarin

Warfarin has been the only oral anticoagulant on the market in the United States for over 50 years. Numerous factors have been identified that affect warfarin dose requirements; however, the effects of obesity have not been established. One retrospective review found that when initiated in hospitalized patients, obese and morbidly obese patients with therapeutic INRs had higher average daily warfarin discharge doses than normal-weight patients; 6.7 mg, 6.7 mg, and 4.4 mg, respectively. Increased time to a therapeutic INR was also noted between normal-weight (6 days), obese (8 days), and morbidly obese patients (10 days). The obese and morbidly obese patients were significantly younger, which could affect the results as elderly patients frequently have lower warfarin requirements.[29]

The recent addition of an oral direct thrombin inhibitor and two Xa-inhibitors expands our oral anticoagulation options. Unfortunately, studies focusing on dosing in obesity are lacking. Dabigatran is approved in the United States for prevention of stroke and systemic embolism in nonvalvular AF.[30] The RE-LY trial noted a 20% decrease in trough concentrations in patients weighing >100 kg; however, dose adjustments have not been recommended.[31] Although not approved for VTE prophylaxis in the United States, a post-hoc analysis compared dabigatran to enoxaparin 40 mg once daily for prevention of VTE in orthopedic surgery patients. No significant difference was noted in the composite end point of major VTE; however, the comparator dose of enoxaparin may be inappropriate for obese patients.[32]

Rivaroxaban is approved for prevention of stroke and systemic embolism in nonvalvular AF, DVT and pulmonary embolism (PE) treatment and reduction of recurrence, and DVT prophylaxis after knee and hip surgery.[33] A phase 2 study demonstrated that a TBW >120 kg was not associated with clinically significant changes in pharmacokinetic or pharmacodynamics parameters; thus, dose adjustments are not warranted.[34] Studies with rivaroxaban have a small proportion of patients with a BMI of >28 kg/m^2 or weights exceeding >100 kg; however, subgroup analyses have shown dose modifications are not needed.[35–37]

"The recent addition of an oral direct thrombin inhibitor and 2 Xa-inhibitors expands our oral anticoagulation options. Unfortunately, studies focusing on dosing in obesity are lacking."

Apixaban is the most recent agent to be approved for prevention of stroke and systemic embolism in nonvalvular AF.[38] One study found that a 10-mg dose of apixaban yielded a 20% decrease in peak concentration in patients weighing >120 kg. The authors concluded that these alterations were not clinically significant and no dose alteration is needed.[39] The ARISTOTLE trial reported weights as greater than or less than 60 kg, so efficacy in obesity cannot be assumed.[40] Although the manufacturers of apixaban state dose adjustment for obese patients is not warranted, the subanalysis of ARISTOTLE has not been published.

As the obesity epidemic continues to affect Americans, we struggle with ensuring adequate therapeutic drug concentrations of anticoagulants while balancing the increased risk of bleeding. Data on appropriate dosing of anticoagulants in obese patients are limited. Dosing of these medications should be based on patient- and drug-specific factors. DT

References available online at www.drugtopics.com.

Editor's note: This article was published first in *Formulary* journal in June.

Katie Buehler *is assistant professor of pharmacy practice, department of pharmacy practice, St. Louis College of Pharmacy, St. Louis; and* **Abigail Yancey** *is associate professor of pharmacy practice, department of pharmacy practice, St. Louis College of Pharmacy, St. Louis.*

NEW DRUG REVIEW Diana M. Sobieraj, PharmD

Doxylamine/pyridoxine returns to market for pregnancy-related nausea, vomiting

In April 2013, FDA approved doxylamine succinate 10 mg, pyridoxine hydrochloride 10 mg (Diclegis, Duchesnay) for the treatment of nausea and vomiting in pregnant women who do not respond to conservative management. Diclegis is a delayed-release formulation combining 10 mg of the antihistamine doxylamine succinate and 10 mg of the vitamin B6 analog pyridoxine hydrochloride. This combination was once marketed in the United States as Bendectin. However, legal suits claiming related birth defects forced the manufacturer to withdraw Bendectin from the market in the 1980s. Diclegis has not been studied in women with hyperemesis gravidarum.

Efficacy

A randomized trial with 261 pregnant women compared doxylamine/pyridoxine to placebo for 14 days. The mean gestational age was 9.3 weeks (range 7 to 14 weeks). Sixty percent of women were taking 4 tablets daily and the remaining 40% were similarly split between 2 and 3 tablets daily. The Pregnancy Unique-Quantification of Emesis (PUQE) score was used to quantify efficacy, and the change in score from baseline to day 15 was evaluated. The PUQE score encompasses information about daily vomiting episodes and feelings of nausea. There was a significant difference in the change of PUQE score from baseline in the doxylamine/pyridoxine group compared to placebo [-0.7 (-1.2 to -0.2)].

Safety

The same randomized trial described above evaluated the safety of doxylamine/pyridoxine. Somnolence was found to be the only adverse event occurring in greater than 5% of participants and of a higher incidence than in the participants receiving placebo. Other adverse events described in the prescribing information include falls or other accidents that can result from the concurrent use of doxylamine/pyridoxine with other central nervous system depressants. Given the risk of somnolence, women should avoid activities such as driving or operation of heavy machinery until medically cleared. Women should also be advised to avoid other depressants of the central nervous system such as alcohol, other antihistamines, narcotics, or sleep aids as these medications may worsen somnolence.

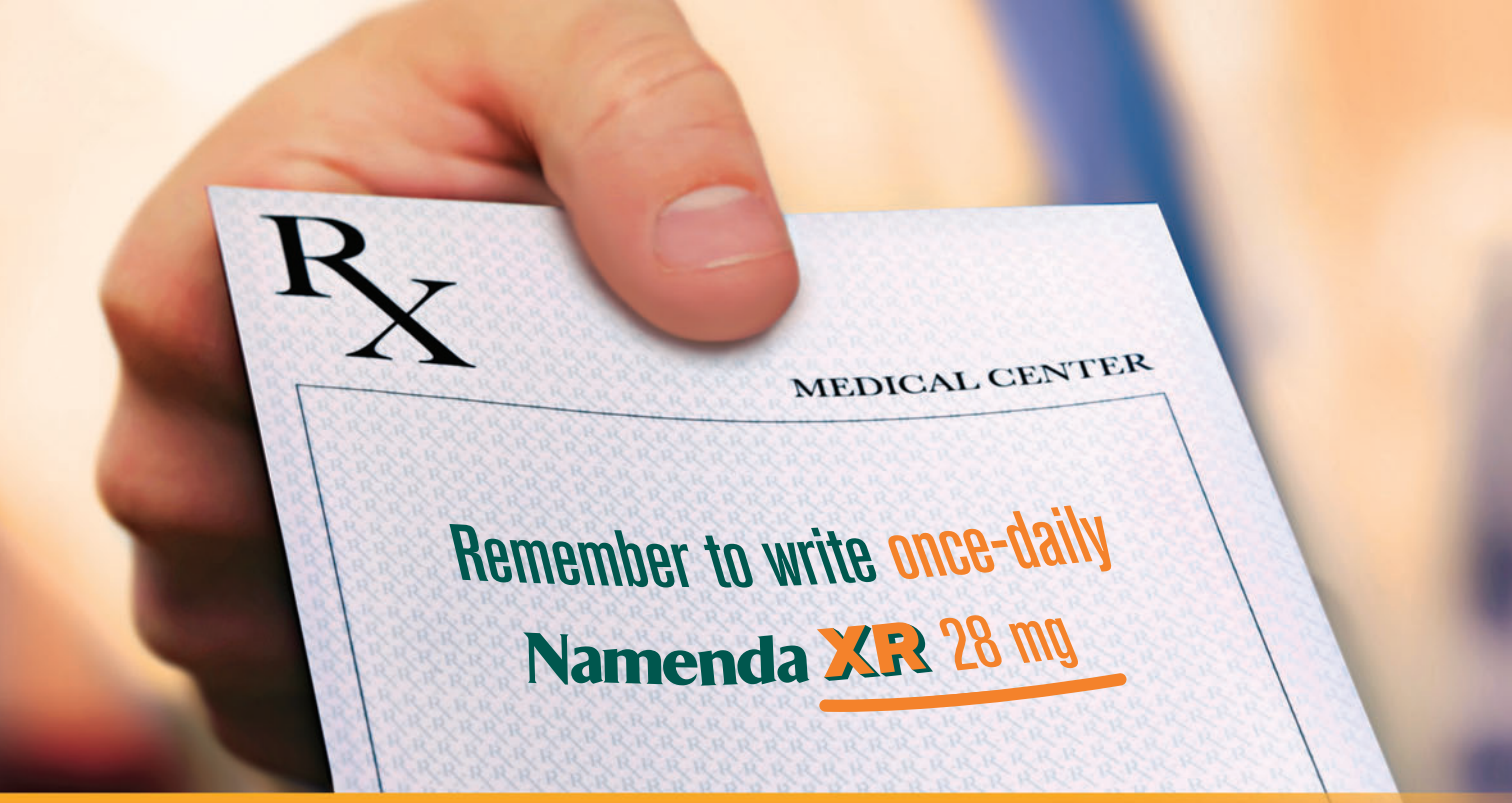
Two meta-analyses based on observational studies from 1963 to 1991 concluded that there was no increased risk of fetal malformation from exposure to doxylamine succinate and pyridoxine hydrochloride in the first trimester.

The voluntary reporting of post-marketing use of 10 mg of doxyamine plus 10 mg of pyridoxine has provided additional possible side effects that may be related to the drug. The following are listed in the package insert: Dyspnea, palpitation, tachycardia, vertigo, vision blurred, visual disturbances, abdominal distension, abdominal pain, constipation, diarrhea, chest discomfort, fatigue, irritability, malaise, hypersensitivity, dizziness, headache, migraines, paresthesia, psychomotor hyperactivity, anxiety, disorientation, insomnia, nightmares, dysuria, urinary retention, hyperhidrosis, pruritus, rash, and maculo-papular rash. Doxylamine/pyridoxine is contraindicated with monoamine oxidase inhibitors since they can prolong the anticholinergic effects of antihistamines. Avoidance of other sedatives is also recommended.

Dosing

Doxylamine/pyridoxine is recognized as a pregnancy Category A drug. The recommended initial dose of doxylamine/pyridoxine is 2 tablets at bedtime on an empty stomach with a glass of water, taken daily and not on an as needed basis. If after two nights symptoms are not adequately controlled, the dose may be increased to 1 tablet in the morning and 2 tablets at bedtime. If on the next day symptoms are still inadequately controlled, the dose can be increased to 1 tablet in the morning, 1 tablet mid-morning, and 2 tablets at bedtime. The maximum recommended dose is 4 tablets daily. It is important to take doxylamine/pyridoxine on an empty stomach due to delayed and reduced absorption. Given the delayed-release formulation these tablets should not be crushed, chewed, or split. There are currently no dose recommendations in patients with renal or hepatic dysfunction as no studies have been conducted in these populations. DT

Diana M. Sobieraj *is assistant professor of Pharmacy Practice, University of Connecticut School of Pharmacy, Storrs, Conn.*



Specify NAMENDA XR 28 mg when prescribing.

NAMENDA XR™ (memantine hydrochloride) extended-release capsules are indicated for the treatment of moderate to severe dementia of the Alzheimer's type.

Important Safety Information

Contraindications

- NAMENDA XR is contraindicated in patients with known hypersensitivity to memantine hydrochloride or to any excipients used in the formulation.

Warnings and Precautions

- NAMENDA XR should be used with caution under conditions that raise urine pH (including alterations by diet, drugs and the clinical state of the patient). Alkaline urine conditions may decrease the urinary elimination of memantine, resulting in increased plasma levels and a possible increase in adverse effects.
- NAMENDA XR has not been systematically evaluated in patients with a seizure disorder.

Adverse Reactions

- The most commonly observed adverse reactions seen in patients administered NAMENDA XR (28 mg/day) in a controlled clinical trial, defined as those occurring at a frequency of at least 5% in the NAMENDA XR group and at a higher frequency than placebo were headache (6% vs 5%), diarrhea (5% vs 4%), and dizziness (5% vs 1%).

Drug Interactions

- No drug-drug interaction studies have been conducted with NAMENDA XR, specifically. The combined use of NAMENDA XR with other NMDA antagonists (amantadine, ketamine, or dextromethorphan) has not been systematically evaluated and such use should be approached with caution.

Dosage and Administration

- The recommended starting dose of NAMENDA XR is 7 mg once daily. The recommended target dose is 28 mg once daily. The dose should be increased in 7 mg increments to 28 mg once daily. The minimum recommended interval between dose increases is one week, and only if the previous dose has been well tolerated. The maximum recommended dose is 28 mg once daily.
- It is recommended that a patient who is on a regimen of 10 mg twice daily of NAMENDA tablets be switched to NAMENDA XR 28 mg once-daily capsules the day following the last dose of a 10 mg NAMENDA tablet. There is no study addressing the comparative efficacy of these 2 regimens.
- It is recommended that a patient with severe renal impairment who is on a regimen of 5 mg twice daily of NAMENDA tablets be switched to NAMENDA XR 14 mg once-daily capsules the day following the last dose of a 5 mg NAMENDA tablet.

Special Populations

- NAMENDA XR should be administered with caution to patients with severe hepatic impairment.
- A target dose of 14 mg/day is recommended in patients with severe renal impairment (creatinine clearance of 5-29 mL/min, based on the Cockcroft-Gault equation).

Please see brief summary of Prescribing Information on the adjacent page.

NEW
Once-Daily

Namenda XR™
(memantine HCl) extended release capsules
7 mg, 14 mg, 21 mg, 28 mg

Forest Pharmaceuticals, Inc.
Subsidiary of Forest Laboratories, Inc.
St. Louis, Missouri 63045

063-13000040 04/13

NAMENDA XR (memantine hydrochloride) extended release capsules
Brief Summary of full Prescribing Information
Initial U.S. Approval: 2003

INDICATIONS AND USAGE: NAMENDA XR (memantine hydrochloride) extended-release capsules are indicated for the treatment of moderate to severe dementia of the Alzheimer's type.

CONTRAINDICATIONS: Hypersensitivity - NAMENDA XR is contraindicated in patients with known hypersensitivity to memantine hydrochloride or to any excipients used in the formulation *[*See *Description in the full Prescribing Information].*

WARNINGS AND PRECAUTIONS: Genitourinary Conditions - Conditions that raise urine pH may decrease the urinary elimination of memantine resulting in increased plasma levels of memantine. **Seizures -** NAMENDA XR has not been systematically evaluated in patients with a seizure disorder. In clinical trials of memantine, seizures occurred in 0.3% of patients treated with memantine and 0.6% of patients treated with placebo.

ADVERSE REACTIONS: Clinical Trial Data Sources - NAMENDA XR was evaluated in a double-blind placebo-controlled trial treating a total of 676 patients with moderate to severe dementia of the Alzheimer's type (341 patients treated with NAMENDA XR 28 mg/day dose and 335 patients treated with placebo) for a treatment period up to 24 weeks. 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. **Adverse Reactions Leading to Discontinuation -** In the placebo-controlled clinical trial of NAMENDA XR [See *Clinical Studies in the full Prescribing Information*], which treated a total of 676 patients, the proportion of patients in the NAMENDA XR 28 mg/day dose and placebo groups who discontinued treatment due to adverse events were 10.0% and 6.3%, respectively. The most common adverse reaction in the NAMENDA XR treated group that led to treatment discontinuation in this study was dizziness at a rate of 1.5%. **Most Common Adverse Reactions -** The most commonly observed adverse reactions seen in patients administered NAMENDA XR in the controlled clinical trial, defined as those occurring at a frequency of at least 5% in the NAMENDA XR group and at a higher frequency than placebo were headache, diarrhea and dizziness. Table 1 in the full Prescribing Information lists treatment-emergent adverse reactions that were observed at an incidence of 2% in the NAMENDA XR treated group and occurred at a rate greater than placebo. The first value displays the percentage of patients in the placebo group (N=335) and the second shows the percentage in the group receiving 28 mg of NAMENDA XR (N=341). **Gastrointestinal Disorders:** Diarrhea (4%, 5%), Constipation (1%, 3%), Abdominal pain (1%, 2%), Vomiting (1%, 2%); **Infections and infestations:** Influenza (3%, 4%); **Investigations:** Weight, increased (1%, 3%); **Musculoskeletal and connective tissue disorders:** Back pain (1%, 3%); **Nervous system disorders:** Headache (5%, 6%), Dizziness (1%, 5%), Somnolence (1%, 3%); **Psychiatric disorders:** Anxiety (3%, 4%), Depression (1%, 3%), Aggression (1%, 2%); **Renal and urinary disorders:** Urinary incontinence (1%, 2%); **Vascular disorders:** Hypertension (2%, 4%), Hypotension (1%, 2%). **Vital Sign Changes -** NAMENDA XR and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, diastolic blood pressure, and weight) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. There were no clinically important changes in vital signs in patients treated with NAMENDA XR. A comparison of supine and standing vital sign measures for NAMENDA XR and placebo in Alzheimer's patients indicated that NAMENDA XR treatment is not associated with orthostatic changes. **Laboratory Changes -** NAMENDA XR and placebo groups were compared with respect to (1) mean change from baseline in various serum chemistry, hematology, and urinalysis variables and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in laboratory test parameters associated with NAMENDA XR treatment. **ECG Changes -** NAMENDA XR and placebo groups were compared with respect to (1) mean change from baseline in various ECG parameters and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in ECG parameters associated with NAMENDA XR treatment. **Other Adverse Reactions Observed During Clinical Trials of NAMENDA XR -** Following is a list of treatment-emergent adverse reactions reported from 750 patients treated with NAMENDA XR for periods up to 52 weeks in double-blind or open-label clinical trials. The listing does not include those events already listed in Table 1, those events for which a drug cause was remote, those events for which descriptive terms were so lacking in specificity as to be uninformative, and those events reported only once which did not have a substantial probability of being immediately life threatening. Events are categorized by body system. **Blood and Lymphatic System Disorders:** anemia. **Cardiac Disorders:** bradycardia, myocardial infarction. **Gastrointestinal Disorders:** fecal incontinence, nausea. **General Disorders:** asthenia, fatigue, gait disturbance, irritability, peripheral edema, pyrexia. **Infections and Infestations:** bronchitis, nasopharyngitis, pneumonia, upper respiratory tract infection, urinary tract infection. **Injury, Poisoning and Procedural Complications:** fall. **Investigations:** weight decreased. **Metabolism and Nutrition Disorders:** anorexia, dehydration, decreased appetite, hyperglycemia. **Musculoskeletal and Connective Tissue Disorders:** arthralgia, pain in extremity. **Nervous System Disorders:** convulsion, dementia Alzheimer's type, syncope, tremor. **Psychiatric Disorders:** agitation, confusional state, delirium, delusion, disorientation, hallucination, insomnia, restlessness. **Respiratory, Thoracic and Mediastinal Disorders:** cough, dyspnea. **Memantine Immediate Release Clinical Trial and Post Marketing Spontaneous Reports -** The following additional adverse reactions have been identified from previous worldwide experience with memantine (immediate release) use. These adverse reactions have been chosen for inclusion because of a combination of seriousness, frequency of reporting, or potential causal connection to memantine and have not been listed elsewhere in labeling. However, because some of these adverse reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship between their occurrence and the administration of memantine. These events include: **Blood and Lymphatic System Disorders:** agranulocytosis, leukopenia (including neutropenia), pancytopenia, thrombocytopenia, thrombotic thrombocytopenic purpura. **Cardiac Disorders:** atrial fibrillation, atrioventricular block (including 2nd and 3rd degree block), cardiac failure, orthostatic hypotension, and torsades de pointes. **Endocrine Disorders:** inappropriate antidiuretic hormone secretion. **Gastrointestinal disorders:** colitis, pancreatitis. **General disorders and administration site conditions:** malaise, sudden death. **Hepatobiliary Disorders:** hepatitis (including abnormal hepatic function test, cytolytic and cholestatic hepatitis), hepatic failure. **Infections and infestations:** sepsis. **Investigations:** electrocardiogram QT prolonged, international normalized ratio increased. **Metabolism and Nutrition Disorders:** hypoglycaemia, hyponatraemia. **Nervous System Disorders:** convulsions (including grand mal), cerebrovascular accident, dyskinesia, extrapyramidal disorder, hypertonia, loss of consciousness, neuroleptic malignant syndrome, Parkinsonism, tardive dyskinesia, transient ischemic attack. **Psychiatric Disorders:** hallucinations (both visual and auditory), restlessness, suicidal ideation. **Renal and Urinary Disorders:** acute renal failure (including abnormal renal function test), urinary retention. **Skin Disorders:** rash, Stevens Johnson syndrome. **Vascular Disorders:** pulmonary embolism, thrombophlebitis, deep venous thrombosis. The following adverse events have been reported to be temporally associated with memantine treatment and are not described elsewhere in the product labeling: aspiration pneumonia, bone fracture, carpal tunnel syndrome, cerebral infarction, chest pain, cholelithiasis, claudication, depressed level of consciousness (including rare reports of coma), dysphagia, encephalopathy, gastritis, gastroesophageal reflux, intracranial hemorrhage, hyperglycemia, hyperlipidemia, ileus, impotence, lethargy, myoclonus, supraventricular tachycardia, and tachycardia. However, there is again no evidence that any of these additional adverse events are caused by memantine.

DRUG INTERACTIONS: No drug-drug interaction studies have been conducted with NAMENDA XR, specifically. **Use with other N-methyl-D-aspartate (NMDA) Antagonists -** The combined use of NAMENDA XR with other NMDA antagonists (amantadine, ketamine, and dextromethorphan) has not been systematically evaluated and such use should be approached with caution. **Effect of Memantine on the Metabolism of Other Drugs -** *In vitro* studies conducted with marker substrates of CYP450 enzymes (CYP1A2, -2A6, -2C9, -2D6, -2E1, -3A4) showed minimal inhibition of these enzymes by memantine. In addition, *in vitro* studies indicate that at concentrations exceeding those associated with efficacy, memantine does not induce the cytochrome P450 isozymes CYP1A2, -2C9, -2E1 and -3A4/5. No pharmacokinetic interactions with drugs metabolized by these enzymes are expected. Pharmacokinetic studies evaluated the potential of memantine for interaction with donepezil (See *Use with Cholinesterase Inhibitors*) and bupropion. Coadministration of memantine with the AChE inhibitor donepezil HCl does not affect the pharmacokinetics of either compound. Memantine did not affect the pharmacokinetics of the CYP2B6 substrate bupropion or its metabolite hydroxybupropion. **Effect of Other Drugs on Memantine -** Memantine is predominantly renally eliminated, and drugs that are substrates and/or inhibitors of the CYP450 system are not expected to alter the pharmacokinetics of memantine. A clinical drug-drug interaction study indicated that bupropion did not affect the pharmacokinetics of memantine. **Drugs Eliminated via Renal Mechanisms -** Because memantine is eliminated in part by tubular secretion, coadministration of drugs that use the same renal cationic system, including hydrochlorothiazide (HCTZ), triamterene (TA), metformin, cimetidine, ranitidine, quinidine, and nicotine, could potentially result in altered plasma levels of both agents. However, coadministration of memantine and HCTZ/TA did not affect the bioavailability of either memantine or TA, and the bioavailability of HCTZ decreased by 20%. In addition, coadministration of memantine with the antihyperglycemic drug Glucovance® (glyburide and metformin HCl) did not affect the pharmacokinetics of memantine, metformin and glyburide. Furthermore, memantine did not modify the serum glucose lowering effect of Glucovance®, indicating the absence of a pharmacodynamic interaction. **Drugs That Make the Urine Alkaline -** The clearance of memantine was reduced by about 80% under alkaline urine conditions at pH 8. Therefore, alterations of urine pH towards the alkaline condition may lead to an accumulation of the drug with a possible increase in adverse effects. Urine pH is altered by diet, drugs (e.g. carbonic anhydrase inhibitors, sodium bicarbonate) and clinical state of the patient (e.g. renal tubular acidosis or severe infections of the urinary tract). Hence, memantine should be used with caution under these conditions. **Drugs Highly Bound to Plasma Proteins -** Because the plasma protein binding of memantine is low (45%), an interaction with drugs that are highly bound to plasma proteins, such as warfarin and digoxin, is unlikely [See *Drug Interactions*]. **Use with Cholinesterase Inhibitors -** Coadministration of memantine with the AChE inhibitor donepezil HCl did not affect the pharmacokinetics of either compound. In a 24-week controlled clinical study in patients with moderate to severe Alzheimer's disease, the adverse event profile observed with a combination of memantine immediate-release and donepezil was similar to that of donepezil alone.

USE IN SPECIFIC POPULATIONS: Pregnancy - Pregnancy Category B: There are no adequate and well-controlled studies of NAMENDA XR in pregnant women. NAMENDA XR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Memantine given orally to pregnant rats and pregnant rabbits during the period of organogenesis was not teratogenic up to the highest doses tested (18 mg/kg/day in rats and 30 mg/kg/day in rabbits, which are 6 and 21 times, respectively, the maximum recommended human dose [MRHD] on a mg/m^2 basis). Slight maternal toxicity, decreased pup weights and an increased incidence of non-ossified cervical vertebrae were seen at an oral dose of 18 mg/kg/day in a study in which rats were given oral memantine beginning pre-mating and continuing through the postpartum period. Slight maternal toxicity and decreased pup weights were also seen at this dose in a study in which rats were treated from day 15 of gestation through the post-partum period. The no-effect dose for these effects was 6 mg/kg, which is 2 times the MRHD on a mg/m^2 basis. **Nursing Mothers -** It is not known whether memantine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when memantine is administered to a nursing mother. **Pediatric Use -** The safety and effectiveness of memantine in pediatric patients have not been established.

DRUG ABUSE AND DEPENDENCE: Memantine is not a controlled substance. Memantine is a low to moderate affinity uncompetitive NMDA antagonist that did not produce any evidence of drug-seeking behavior or withdrawal symptoms upon discontinuation in 3,254 patients who participated in clinical trials at therapeutic doses. Post marketing data, outside the U.S., retrospectively collected, has provided no evidence of drug abuse or dependence.

OVERDOSAGE: Signs and symptoms most often accompanying overdosage with other formulations of memantine in clinical trials and from worldwide marketing experience, alone or in combination with other drugs and/or alcohol, include agitation, asthenia, bradycardia, confusion, coma, dizziness, ECG changes, increased blood pressure, lethargy, loss of consciousness, psychosis, restlessness, slowed movement, somnolence, stupor, unsteady gait, visual hallucinations, vertigo, vomiting, and weakness. The largest known ingestion of memantine worldwide was 2 grams in an individual who took memantine in conjunction with unspecified antidiabetic medications. This person experienced coma, diplopia, and agitation, but subsequently recovered. One patient participating in a NAMENDA XR clinical trial unintentionally took 112 mg of NAMENDA XR daily for 31 days and experienced an elevated serum uric acid, elevated serum alkaline phosphatase, and low platelet count. No fatalities have been noted with overdoses of memantine alone. A fatal outcome has very rarely been reported when memantine has been ingested as part of overdosing with multiple drugs; in those instances, the relationship between memantine and a fatal outcome has been unclear. Because strategies for the management of overdose are continually evolving, it is advisable to contact a poison control center to determine the latest recommendations for the management of an overdose of any drug. As in any cases of overdose, general supportive measures should be utilized, and treatment should be symptomatic. Elimination of memantine can be enhanced by acidification of urine.

Manufactured for:
Forest Pharmaceuticals, Inc.
Subsidiary of Forest Laboratories, Inc.
St. Louis, MO 63045

Manufactured by:
Forest Laboratories Ireland Ltd

Licensed from Merz Pharmaceuticals GmbH

Revised: April 2013

62-12000315-BS-A-RMC8791-APR13

Please also see full Prescribing Information at www.namendaxr.com

ANTICOAGULATION THERAPIES Anna D. Garrett, PharmD, BCPS

Time to effective platelet inhibition extended with ticagrelor, prasugrel

In a study comparing ticagrelor and prasugrel in patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary PCI, prasugrel was shown to be non-inferior to ticagrelor in terms of residual platelet reactivity measured 2 hours after the loading dose. The study also demonstrated that 4 hours is needed to achieve effective platelet inhibition in most patients. Only half of treated patients achieved effective platelet inhibition 2 hours after receiving the drugs.

In the pharmacodynamic study, 25 STEMI patients undergoing primary PCI with bivalirudin were randomized to receive a 60-mg loading dose of prasugrel, and 25 patients were randomized to receive a 180-mg loading dose of ticagrelor. At 2 hours after the dose, 44% of patients treated with prasugrel and 60% of those treated with ticagrelor had high residual platelet reactivity (HRPR). For those treated with prasugrel and ticagrelor, the time required to achieve a PRU <240 was 3 hours and 5 hours, respectively. The use of morphine significantly affected the activity of prasugrel and ticagrelor, with morphine use shown to be an independent predictor of HRPR 2 hours after the loading doses were administered.

The results suggest a significant time window after primary PCI in which many patients are at high risk of stent thrombosis.

Source: Parodi G, Valenti R, Bellandi B et al. Comparison of prasugrel and ticagrelor loading doses in ST-segment elevation myocardial infarction patients: RAPID (Rapid Activity of Platelet Inhibitor Drugs) primary PCI study. J Am Coll Cardiol. *2013;61(15):1601–1606.*

Tenecteplase plus heparin improves outcomes in PE

Adding tenecteplase to standard treatment with heparin in patients with intermediate-risk pulmonary embolism (PE) significantly reduced mortality or hemodynamic collapse, according to the PE Thrombolysis Study (PEITHO). However, patients are at increased risk of major hemorrhage.

This trial, which was conducted in 1006 patients with a mean age of 70 years, is the largest for this indication. Patients received heparin plus placebo or heparin plus a weight-based bolus of tenecteplase. The primary end point was death from any cause or hemodynamic collapse after seven days.

The primary end point was reduced in patients treated with tenecteplase and heparin, compared with the heparin-only group (2.6% vs 5.6%, respectively). However, major bleeding was significantly increased with tenecteplase compared to placebo (6.3% vs 1.5%, respectively). According to an analysis by age, the combination is safest relative to bleeding risk in patients less than 75 years.

Tenecteplase is not FDA-approved for use in patients with acute PE, but other thrombolytic agents such as streptokinase, alteplase, and urokinase, may be used.

Source: Nainggola L. PEITHO: Persuasive for thrombolysis in PE? http://www.theheart.org/article/1517447.do. *Accessed April 28, 2013.*

Effect of hemodialysis on dabigatran

A drawback to the use of novel anticoagulants is the lack of a reversal agent in emergent situations. Dabigatran, a direct thrombin inhibitor, is commonly used to prevent strokes in patients with atrial fibrillation. In a recent, open-label, phase I trial, investigators studied the pharmacokinetics, pharmacodynamics, and safety of dabigatran before, during, and after 4-hour hemodialysis sessions with either 200 or 400 mL/min targeted blood flow in 7 end-stage renal disease patients.

Dabigatran was administered over 3 days in a regimen designed to achieve peak plasma concentrations comparable to those observed in atrial fibrillation patients receiving 150 mg twice daily. Plasma concentration-time profiles were similar in both periods on day 3. Four hours of hemodialysis removed almost 50% and 60% of total dabigatran from the central compartment with 200 and 400 mL/min targeted blood flow, respectively. The anticoagulant activity of dabigatran was linearly related to its plasma levels. There was a minor redistribution of dabigatran (<16%) after the end of the hemodialysis session. These results demonstrate that hemodialysis can be useful to eliminate dabigatran in emergency situations.

Source: Khadzhynov D, Wagner F, Formella S et al. Effective elimination of dabigatran by haemodialysis. A phase I single-centre study in patients with end-stage renal disease. Thromb. Haemost. *2013;109:596–605.* DT

Anna D. Garrett *is a clinical pharmacist and president of Dr. Anna Garrett, a health and wellness coaching company in Asheville, N.C.*

CPE CREDIT: 2.0

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

EDUCATIONAL OBJECTIVES

Goal: To assist pharmacists in understanding the regulatory and ethical issues related to opioid pain management.

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

- **Describe the process of evaluating opioid analgesic use in high-risk populations**
- **Discuss how to identify and address aberrant opioid analgesic use behaviors**
- **Describe the utility of state prescription monitoring programs (PMP)**
- **Describe the utility of a pain agreement, screening for risk of addiction, urine drug testing**
- **Discuss the role of an interdisciplinary team approach in the management of pain**

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 knowledge-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.

AACPE # 0009-9999-13-009-H03-P

Grant Funding: Supported by an educational grant from Purdue Pharma, L.P.

Activity Fee: There is no fee for this activity.

Initial release date: 7/10/2013

Expiration date: 7/10/2015

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*

Regulatory and ethical issues in pain management

Lisa M. Holle, PharmD, BCOP
ASSISTANT CLINICAL PROFESSOR, UNIVERSITY OF CONNECTICUT SCHOOL OF PHARMACY, STORRS, CONN.

Kevin W. Chamberlin, PharmD
ASSISTANT CLINICAL PROFESSOR AND ASSISTANT DEPARTMENT HEAD, PHARMACY PRACTICE, UNIVERSITY OF CONNECTICUT SCHOOL OF PHARMACY, STORRS, CONN.

Abstract

Despite the rise in awareness of the risks of abuse, misuse, addiction, and diversion associated with opioid use in the treatment of pain, healthcare professionals can minimize the risks through appropriate assessment and an individualized approach to treatment. Understanding high-risk behaviors associated with chronic opioid therapy and implementing screening of all patients can aide the healthcare professional in selecting the most appropriate treatment plan for a patient. Pain agreements, urine drug screening, and monitoring the 4 "As"—analgesia, activities of daily living, adverse effects, and aberrant drug-related behavior—can minimize the risks and aide in early recognition of potential development of misuse or addiction. An interdisciplinary team approach to pain management has been shown to be effective in improving efficacy, minimizing risk misuse/addiction, and is cost-effective. The pharmacist can play an important role in the interdisciplinary team.

Faculty: Lisa M. Holle, PharmD, BCOP and Kevin W. Chamberlin, PharmD
Dr. Holle is assistant clinical professor, University of Connecticut School of Pharmacy, Storrs, Conn. Dr. Chamberlin is assistant clinical professor and assistant department head, Pharmacy Practice, University of Connecticut School of Pharmacy, Storrs, Conn.

Faculty Disclosure: Dr. Holle and Dr. Chamberlin 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 University of Connecticut School of Pharmacy. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.

IMAGE: GETTY IMAGES / PHOTODISC / STEVE ALLEN

Pain Management Considerations in Medication Therapy Management CPE Series

Welcome to the CPE series, Pain Management Considerations in Medication Therapy Management, which has been designed for pharmacists in all areas of practice who need to further their clinical and MTM skills in the management of patients with pain. From April to August 2013, pharmacists can earn up to 10 hours of CPE credit with 5 monthly knowledge-based activities from the University of Connecticut School of Pharmacy and *Drug Topics*.

This month, the professional development activity will cover regulations and ethical issues in pain management. Next month, the knowledge-based activities will conclude with management of common pain conditions by pharmacists, including osteoarthritis, low back pain, fibromyalgia, sprains, strains, and contusions, and generalized headaches.

The Pain Management series will also be offering application-based activities for an additional 2 CPE credits. Online interactive case-based studies will be available with 1 hour of CPE credit, starting in September and continuing in October 2013.

Chronic pain is a major health problem in the United States and is expected to increase due to the aging population, increased incidence of conditions associated with chronic pain, and a greater understanding of pain syndromes.[1] Opioids, an essential therapeutic option for the treatment of chronic pain, are now widely available as a result of improved awareness and treatment of chronic pain. Although much can still be done to improve access to appropriate pain management therapies for chronic pain, opioid prescribing is at its highest level in decades.

Opioids, like any chronic medications, are not without risks. Side effects of opioid therapy, including nausea, vomiting, dizziness, sweating, constipation, sedation, and respiratory depression, can largely be prevented in patients who have undergone appropriate assessment, prescribing, and management with supportive care therapies. Other negative consequences, most notably the risk of abuse, misuse, addiction, and diversion, have risen in prevalence along with the improved access to these medications. In fact, opioids have become the most misused drug in the United States, second only to marijuana, resulting in a rise in analgesic-related emergency department visits and unintentional overdoses.[2,3] In 2011, 1.8 million opioid analgesic users met the diagnostic criteria of dependence or abuse, and a recent meta-analysis estimated that 3.3% of chronic pain patients were addicted to opioids.[3,4] These risks, however, can be minimized with an individual approach to opioid prescribing that includes an assessment of the patient's health status and risk factors, optimization of drug administration, and ongoing monitoring of therapy by an interdisciplinary team.

The ABCDE Characteristics of Addiction

Inability to consistently **Abstain**; Impairment in **Behavioral** control; **Craving** or increased "hunger" for drugs or rewarding experiences; **Diminished** recognition of significant problems with one's behavior and interpersonal relationships; and A dysfunctional **Emotional** response.

Evaluation of high-risk behaviors for chronic opioid therapy

Current evidence suggests that addiction prevalence in patients with pain may be no different than prevalence of addiction in the general population.[5,6] Several variables have been associated with a higher risk of misuse, abuse, and addiction when opioids are used in the treatment of chronic pain (**Table 1**).[7-10]

Each candidate for opioid therapy should undergo a comprehensive assessment of medical conditions that may increase the risk of physical adverse events of opioid therapy and physiologic/behavioral/genetic predispositions that may result in tolerance, withdrawal, physical or psychologic dependence, abuse, or addiction. Comprehensive assessment and documentation before initiating opioid therapy is recommended for all individuals. This should include a thorough history and physical examination and documentation about general health, psychosocial history, psychiatric status, and substance abuse history.[11]

Screening for risk of addiction

The American Society of Addiction Medicine (ASAM) defines addiction as "a primary, chronic disease of brain reward, motivation, memory and related circuitry."[12] ASAM offers an acronym, ABCDE, to assist in identifying characteristics common with addiction:

- Inability to consistently Abstain;

TABLE 1

RISK FACTORS OF OPIOID MISUSE, ABUSE, AND ADDICTION WITH CHRONIC OPIOID USE

• History of addiction (alcohol or drugs) in biologic parents
• Current drug addiction in family
• Regular contact with high-risk groups or activities (eg, drug-using friends)
• Smoking
• Personal history of illicit drug use (eg, >4 cannabis joints/wk, use of street drugs, acquire psychoactive prescriptions from sources other than physicians) or alcohol addiction
• Current use of illicit drugs or significant alcohol use
• Psychiatric comorbidities
• Age <40 years

Source: Ref 7-10

• Impairment in Behavioral control;

• Craving or increased "hunger" for drugs or rewarding experiences;

• Diminished recognition of significant problems with one's behavior and interpersonal relationships; and

• A dysfunctional Emotional response.

Like other chronic diseases, addiction cycles between abstinence and relapse. Addiction is a progressive disorder. Genetic disorders can account for up to half of the likelihood that an individual will develop addiction. Environmental triggers and cultural acceptance of addiction, coupled with biologic alterations, will impact whether and to what extent an individual may develop an addictive personality.

Screening for alcohol and/or drug misuse is crucial to prevention of or early intervention in addiction.[12] Several screening tools specific to prescription opioid abuse are available, although limited evidence exists on the reliability and accuracy of each. Despite this, screening tools can play a role in helping to identify high-risk patients. Some tools include: Screener and Opioid Assessment for Patients with Pain (SOAPP), Opioid Risk Tool (ORT), Pain Medication Questionnaire (PMQ), Prescription Drug Use Questionnaire patient version (PDUQP), Diagnosis, Intractability, Risk, and Efficacy inventory (DIRE), Addiction Behaviors Checklist (ABC), and Atluri and Sudarshan tool. The first 4 tools (SOAPP, ORT, PMQ, and PDUQP) rely on the patient providing truthful answers, whereas the remaining tools (DIRE, ABC, and Atluri and Sudarshan) incorporate objective and subjective information. Each of these tools evaluates slightly different high-risk abuse criteria, but includes items such as family and personal history of substance abuse, age, patient involvement with pain management, psychologic health, chemical health, reliability, social support, and efficacy of pain medications.[11-20]

Whether screening tools are used, a thorough patient interview is conducted, or a combination of these is performed patients can be classified into 3 categories: low risk, medium risk, or high risk of potential for misuse or abuse (**Table 2**).[11,20] Screening patients will not only provide insight on the potential for addiction or abuse but will also help determine opioid management strategies, including frequency of monitoring. Other mechanisms for providers to evaluate the potential for abuse or addiction is to obtain data from a prescription monitoring program (PMP) and/or initiate urine drug testing.

Prescription monitoring programs (PMPs)

PMPs allow prescribers and pharmacists to access a patient's prescription information. First and foremost, a PMP is not intended to prevent patients from obtaining necessary medications; rather, a PMP is intended primarily to be a source of information for prescribers and pharmacists to use in the care of patients and as a tool to help deter, detect, and appropriately respond to drug diversion and abuse for prescription controlled substances (**Table 3**).[21] These licensed healthcare professionals must register for access with the sponsoring agency within their state. According to the State Pain Policy Advocacy Network, 49 states and Guam either have operating PMPs or have enacted legislation to implement them. Missouri remains as the lone state without a PMP or pending legislation. Further, there exists the PMP Information Architecture (PMIX) to enable the exchange of PMP data between states.[22] To qualify for participation in PMIX, a state must demonstrate that it has: legislation enabling it to share live patient data with other states, identified at least 1 other state to serve as an exchange partner, and a memorandum of understanding to share with the identified exchange partner(s).

A recent report suggests that a substantial proportion of the illegal channeling of prescription opioids through dealers originates in healthcare sources, including: pain clinics, "connections" in pharmacies and healthcare facilities, and purchasing medications from indigent patients.[23] PMPs can provide useful feedback and information to prescribers on their own prescribing trends. Such information can help prescribers obtain patient drug histories, provide assurance to prescribers who suspect a patient may be noncompliant regarding prescription use, and assist in identifying patients for early assessment and treatment. In addition to the aforementioned reasons, the public health community can use information from the PMP to monitor trends and address prescribing problems. With more than 200 million opioid prescriptions issued nationwide each year, and approximately 16,000 related deaths annually from prescription opioid overdose, the hope is to deter prescribers, dispensers, and consumers from participating in illegal drug diversion schemes by knowing a PMP is in place and information is tracked and shared.[24]

Urine drug testing

It is recommended that urine drug testing be conducted on a random basis to remain effective at its intention of being part of the whole pain regimen review process.[25] Randomness also eliminates any

TABLE 2

RISK STRATIFICATION AND MONITORING FOR CHRONIC OPIOID THERAPY

Risk group	Characteristics	Monitoring recommendations
Low risk	• Physical pathology of pain • Objectives signs/reliable symptoms • Clinical correlation with diagnostic tests • ± Mild psychologic comorbidities • ± Coexisting medical conditions • No or well defined and controlled personal/family alcoholism or substance abuse • Age ≥45 years • High pain level acceptance and active coping strategies • Well-motivated and willingness to participate in multimodality treatment and attempt to function at normal levels	• Urine drug testing: every 1-2 years • PMP: twice yearly • Dose limit not needed • If aberrant behaviors are demonstrated: counseling to address; if unchanged, reconsider opioid use
Medium risk	• Significant pain with objective signs/symptoms confirmed by radiologic, physical, or diagnostic exams • Moderate psychologic problems • Well-controlled medical conditions, which are not affected by chronic opioid therapy (eg, sleep apnea) • Mild tolerance but not hyperalgesia without physical dependence or addiction • Past history of personal/family alcoholism or substance abuse • Pain involvement of >3 body regions • Defined pain pathology of moderate levels of pain acceptance and coping strategies • Willing to participate in multimodal therapy and attempting to function in normal daily activities	• Urine drug testing: every 6-12 mo • PMP: 3 times yearly • Dose limit - consider • If aberrant behaviors are demonstrated: counseling to address; if unchanged, reconsider opioid use
High risk	• Widespread pain without objective signs/symptoms (involves >3 body regions) • Aberrant drug-related behavior • History of misuse, abuse, addiction, diversion, dependency, tolerance, hyperalgesia, and alcoholism • Major psychologic disorders • Age <45 years • HIV-related pain • High levels of pain exacerbation and low coping strategy levels • Unwilling to participate in multimodal therapy • Unable to function close to near normal lifestyle	• Urine drug testing: every 3-6 mo • PMP: 4 times yearly • Dose limit – consider low doses and reassess risk/benefit before dose escalations • If aberrant behaviors are demonstrated: wean off opioids OR work with addiction specialist

Abbreviations: PMP, prescription monitoring program

Source: Ref 11, 20

patient feeling singled out or "targeted," and allows for the collection of a true representative sample over time to assist with patient evaluation.[26] The rationale behind urine drug monitoring in the outpatient setting is inclusive of the following: to confirm that the patient is taking the prescribed medication, to detect diversion of the prescribed medication, to detect the presence of illicit, nonprescription medication(s), and for workplace drug testing programs.

Accurate self-reporting by patients of drug misuse, diversion, or illicit substance use is often unreliable and underreported.[25,27] One study looking at more than 800 chronic opioid patients found that nearly 25% used illicit substances, yet nearly half denied substance abuse despite being guaranteed anonymity in the survey.[28] To be useful, however, the results of urine toxicology screenings must also be appropriately interpreted. Another study demonstrated that primary care physicians do poorly at this, with none of the 80 physicians answering all survey questions correctly and only 20% answering even half of the questions correctly on what was considered a rudimentary toxicology survey.[29]

Qualitative analysis. The most commonly used method of urine drug testing is that done by qualitative analysis, which is often less expensive and more efficient to run in-house at most hospitals and/or laboratories. Quantitative analysis is also available; however, this often requires that the specimen be sent to a regional laboratory, resulting in a 1- to 3-day lag time in reporting. Qualitative analysis for urine drug monitoring is antibody based and enzyme mediated. Anti-drug antibody is added to the urine sample and, if the drug is present, the antibody binds to the drug and allows a measurable indicator reaction resulting in a "positive" report.[30,31] Quantitative analysis, which utilizes gas chromatography followed by mass spectroscopy, is considered the gold standard, as it is 99% sensitive and 99% specific.[30] Definitions for qualitative analysis interpretation are available in **Table 4.**[32] Cut-off values for detection for each class of medications are set by the United States Department of Health and Human Services (DHHS) that defines a positive result in the workplace.[33] DHHS mandates that federal employees and federally related industries have urine

TABLE 3

USEFUL INFORMATION FROM A PATIENT-SPECIFIC PMP REPORT

Aliases and previous addresses
Payment methods, including: cash, Medicaid, private third party for each reported medication
Prescriber information (including address) for each reported medication
Dispensing pharmacy information (including address) for each reported medication

Abbreviation: PMP, prescription monitoring program

Source: Ref 21

testing that includes 5 drugs of abuse: amphetamines, cannabinoids, cocaine, opioids, and phencyclidine (PCP).

The 4 most common classes of medications screened for by urine toxicology are benzodiazepines, opioids, cocaine metabolites, and cannabinoids. This next section defines the reagents that are being tested for within each class, common cut-off values used, the length of time detectable after consumption, and any unique nuances to specific drugs within the class.

Benzodiazepines. The DHHS guidelines do not mandate benzodiazepines as 1 of the 5 drugs of abuse to be urine tested for in the workplace; however, benzodiazepines are often abused for their euphoric effects. Benzodiazepines differ primarily in pharmacokinetic parameters such as half-life, metabolites, and onset; these attributes are what typically lend to their potential for abuse. Although all benzodiazepines have abuse potential, those with higher potency and shorter half-lives (e.g., alprazolam, triazolam) and greater lipophilicity (e.g., diazepam) share the greatest risk of abuse.[34] Detection in the urine of benzodiazepines by various commercially available assays testing for benzodiazepine-glucuronides is typically based on the identification of oxazepam being present, an end metabolite of many benzodiazepine drugs.[35,36] The standard (federally mandated) level for benzodiazepine detection is at 300 ng/mL.[35] Benzodiazepines not metabolized to oxazepam tend to have higher cut-off values (e.g., alprazolam, clonazepam), excluding triazolam. Highly lipophilic benzodiazepines such as diazepam are detected in the urine within 36 hours.[35] Agents that are extensively metabolized with long half-lives such as diazepam and chlordiazepoxide can be detectable in the urine for up to 30 days post ingestion. Of note, common hypnotics such as zolpidem, zaleplon, and eszopiclone, although benzodiazepine-like, are not true benzodiazepines. These hypnotic agents are typically not identified on standard urine drug screens and must be individually requested for detection.

Opioids. Urinalysis testing for opioids—prescription or illicit—typically targets the detection of morphine. Synthetic (e.g., fentanyl, methadone) and semisynthetic opioids (e.g., oxycodone, oxymorphone, hydromorphone, hydrocodone) typically will have higher cut-off values, or show up as false negatives because the levels are below the standardized cut off of 2000 ng/mL.[33] Five to 13% of codeine is metabolized via cytochrome P450-2D6 and O-demthylation to morphine, and so testing for morphine will identify those ingesting codeine and morphine.[35] Synthetic (e.g., fentanyl, methadone) and semisynthetic opioids (e.g., oxycodone, oxymorphone, hydromorphone, hydrocodone) do not have a direct metabolism to codeine or morphine, and so typically will have higher cut-off values, or show up as false negatives, because the levels are below the standardized cut off of 2000 ng/mL.[33] The federal standard was changed in 1998 from a much lower level of 300 ng/mL to limit the false-positive results from poppy-seed ingestion; however, most clinical laboratories continue to use the lower cut off to allow for greater sensitivity in detecting opioid use.[37] Detection times for opioids range from first appearance in the urine within 1 hour of ingestion to 60 hours post ingestion for the latest detection.[38] Quinolones like levofloxacin and ofloxacin have been described in various case reports as having false-positive results for opioid urine tests as a result of cross-reacting with the reagent used in qualitative analysis.[37] Rifampin has also been shown to cause a false-positive result for opioids on urine screening.[39]

Cocaine. The primary metabolite of cocaine is benzoylecgonine, and urine screens detect it as representative of cocaine use. The standard cut off for cocaine is defined as 300 ng/mL by DHHS.[33] Benzoylecgonine can be detected in the urine after ingestion of cocaine for 2 to 4 days. Passive consumption of cocaine smoke in a heavily contaminated environment has been shown to cause positive cocaine screen results in children.[40] Low doses of cocaine are typically identifiable in urine for 1 to 2 days; heavier, chronic users may have detection times of 2 to 3 days.[41] In chronic, heavy consumers of cocaine detection as far as 22 days after ingestion has been reported.[42]

Cannabinoids. Cannabis is identified by testing for the reagent presence of 11-nor-delta-9-tetrahydrocannabinol-9-carboxylic acid (9-carboxy-THC) and other metabolites of THC in the urine. The standard cut off for marijuana metabolites is 50 ng/mL.[33] The high lipophilicity of cannabis causes extensive deposition and storage of THC in adipose tissue throughout the body and results in a

Pause&Ponder

A new patient arrives at your community pharmacy with a prescription for sustained-release oxycodone 10 mg every 12 hours #60. What tools do you have at your practice site to assess whether this patient is at high risk of aberrant behavior before filling the prescription?

slow excretion of the drug into the urine. A single use of cannabis can produce positive urine screens up to 1 week after ingestion, and long-term use has been detected in the urine as many as 46 days post consumption.[43] Passive exposure to low-levels or limited marijuana smoke will test positive infrequently; however, passive exposure to high-level marijuana smoke (>16 marijuana cigarettes) will give high levels of urinary excretion of cannabinoid metabolites.[44]

Quantitative analysis. Positive and negative samples can have quantitative analysis performed (or be sent to a reference laboratory to be completed). Quantitative analysis will allow for the testing of compounds that may be below the limit of detection, and to confirm or differentiate between true positives and false positives. Quantitative analysis of previously run qualitative analysis specimens also can test for compounds not detected by standard qualitative means (true negatives). Additionally, quantitative analysis can provide identification of specific compounds in the case of true positives (e.g., heroin, codeine, morphine), and even help qualify if a patient's positive cannabinoid result is from active or passive inhalation. Regardless of the testing method employed, proper interpretation of a urine toxicology screen is often nonspecific and must be taken into clinical context with the whole patient presentation.

Dose limitations

Recently, the results of 5 studies showed that the rate of overdose is directly proportional to the prescribed opioid dose. An additional study reported that the difference is even higher in patients with a substance abuse history. The doses in these studies related to an emergency department admission or death ranged from 40-mg morphine-equivalent dose up to 200-mg morphine-equivalent dose. A call for establishing a maximum daily dose to guide prescribers in treatment patients with chronic pain has been made, but this is still considered controversial. Many believe that chronic pain is undertreated and that by requiring dose limitations, some patients will be left inadequately treated.[45-49]

TABLE **4**

QUALITATIVE ANALYSIS DEFINITIONS

True positive	The compound for which the reagent is specific is present in the urine and is positive via qualitative analysis.
True negative	The compound for which the reagent is specific is not present in the urine and is negative via qualitative analysis.
False positive	The compound for which the reagent is specific is not present in the urine and is positive via qualitative analysis.
False negative	The compound for which the reagent is specific is present in the urine and is negative via qualitative analysis.

Source: Ref 32

Addressing aberrant opioid analgesic use behaviors

For a list of aberrant drug-related behaviors, see **Table 5**.[11] Screening, urine drug testing, pain agreements, monitoring, and open communication have all been described as methods for addressing aberrant behaviors and treating pain in patients with an addictive history.[50]

To help monitor the use of drugs, both prescription and recreational, some prescribers ask patients to sign pain agreements or opioid treatment agreements.

Pain agreements. To help monitor the use of drugs, both prescription and recreational, some prescribers ask patients to sign pain agreements (sometimes referred to as pain contracts or opioid treatment agreements). Such agreements spell out that the patient agrees only to use a single pharmacy for all of their pain medications, to refuse pain medications from another provider, and to submit to random blood and/or urine drug tests. These agreements may be voided if the patient does not follow the rules, and prescribers may drop the patient from their practice.

Although some believe that pain agreements can invade a patient's privacy and damage the patient-provider trust relationship, many prescribers believe that such an agreement gives the patient an opportunity to help her/himself. Physicians in Washington state, for example, who treat chronic pain patients, are required to use treatment agreements when prescribing opioids to patients with a history of substance abuse or psychiatric illness. Furthermore, these Washington physicians must seek specialist consultation when prescribing doses greater than 120 mg of morphine (or equivalent) daily.[51] The idea is that patients with a substance abuse history or traits of an addictive personality may be more inclined to abuse opioids and a pain agreement allows for the prescriber to have a protocol to follow if it is believed that the patient may be straying off said agreement.

Monitoring therapy. Once a patient starts opioid therapy, the "4 As" should be monitored: analgesia (pain relief), activities of daily living (physical and social functioning), adverse effects, and aberrant (or nonadherent) drug-related behaviors.[52,53] The role of adherence monitoring should be continued and includes PMPs, urine drug testing, pill counts, and behavioral assessments at each visit. Particulars about adherence monitoring are based on risk stratification (**Table 2**).[11,20]

If addiction is suspected, further assessment of aberrant drug behaviors and possible causes is as important as increasing monitoring and care. This can be accomplished by querying the PDM database, requiring unscheduled visits with medication counts, performing urine drug testing, initiating a dialogue with the

TABLE 5

ABERRANT DRUG-RELATED BEHAVIORS

Alternation of prescriptions or route of delivery
Doctor shopping or accessing opioids from other sources
Multiple unauthorized dose escalations
Drug-seeking behavior with focus on certain types of opioids and benzodiazepines
Loss of prescriptions
Requests for early refills
Aggressive complaining
Staff harassment
Complaining about other patients
Questioning rights and responsibilities
Repeated withdrawal symptoms
Exacerbation of underlying mood or anxiety disorders
Alcohol use
Poor social functioning
Loss of job and loss of activities of daily living
Emphatic views on opioid medication and illicit drugs as well as legalization of drugs

Source: Ref 11

patient, and obtaining permission to involve family members or other caregivers if needed. In all instances, documentation of action is important.[10] Initiating a discussion with the patient about potentially aberrant drug-taking behaviors can be difficult, but it provides very useful information. It is best to take a nonjudgmental stance, making it a fact-finding mission rather than an inquisition. This will allow the patient to be more forthcoming. Start with sweeping questions about general attitudes (How helpful has your medication been for you? Have you had any bad outcomes?). Avoid yes/no questions to allow the patient to open up and share their perspective. Being curious and interested in your patient will often help the patient to reveal how they use their medicine and what it means in their daily lives (e.g., use to cope with stress instead of pain relief). After the open dialogue is started, question the patient looking for signs of self-medication and chemical coping (Have you ever taken pain medications for other reasons? Have you ever taken them to help you sleep?). Building on those questions, determine how central the medications are to the patient's life. Exploring how open the patient is to alternative forms of pain therapy such as relaxation therapy and interventional procedures will allow you to have a full understanding about how to consider changes to opioid therapy.[54]

Intensifying monitoring and care can also be pivotal with early identification of suspected addiction development. Reviewing the pain agreement with patient/family can re-emphasize the expectations of treatment and consequences of aberrant drug taking. With each prescription, communicate with the patient that this will be logged in the state PMP, which may deter aberrant behavior. Prescribing a limited supply, for example, of 1 week, will require the patient to make frequent visits for assessment both of pain relief and aberrant behaviors. Also requiring the patient to bring leftover medication to the clinic for pill counts can allow for appropriate adherence monitoring. Referral to an addiction medicine specialist or facility to assist in care can also be considered.

Opioid treatment in high-risk patients

For high-risk patients who are currently addicted to alcohol or other drugs, it is usually recommended to withhold opioid therapy for pain conditions until the addiction is treated and in remission.[9] Not only does prescribing opioids to patients with an addiction increase the possibility of drug diversion and opioid-seeking behaviors, but often pain perception and functioning are improved following addiction treatment. However, in patients with a past history of addiction, opioid therapy can be used when nonopioid therapy is unsuccessful. It is suggested that prescribing small amounts, titrating slowly, performing frequent urine drug testing, and avoiding potent opioids (e.g., oxycodone and hydromorphone) is recommended to minimize drug diversion.

In patients with suspected opioid misuse and an identified pain condition requiring opioid therapy, a trial of structured opioid therapy may be useful.[9,55] If a patient has a history of injecting or crushing tablets, addiction treatment should instead be considered. The basis for structured opioid therapy is frequent dispensing of long-acting opioids that allows for frequent monitoring. It is recommended that dispensing occurs daily, alternate days, or at most twice per week, with continual pill or patch counts. Long-acting preparations are preferred rather than parenteral or short-acting preparations. Urine drug tests should be done 1 to 4 times monthly. Avoiding oxycodone and hydromorphone is preferred because of their high abuse potential, although opioid-deterrent preparations may be considered (see below). Structured opioid therapy is most successful when conducted by an interdisciplinary team. If patients continue to show aberrant behavior (e.g., running out of medications early), referral for opioid-agonist treatment or abstinence treatment is recommended.

Opioid formulations that incorporate pharmacologic strategies and physical barriers to deter or resist misuse and abuse are also an option in this population.[56,57] Addition of physical barriers to extended-release opioid products make extracting the active drug from its formulation more difficult (e.g., oxymorphone [Opana] and hydromorphone [Exalgo]). Another strategy to deter abuse is including an opioid antagonist with an opioid product (e.g., buprenorphine/naloxone [Suboxone]). With opioid agonists/antagonists, a patient may experience withdrawal symptoms if the product is altered and administered by another route of administration, such as intravenously or intramuscularly. Although this buprenorphine/naloxone is marketed for patients with opioid dependence, it may be an alternative to a structured opioid regimen in some patients with a history of substance abuse in which opioid therapy is warranted.

Pain management is not immune to the concern that guidelines alone may

have only a modest effect on practice.[58]

Some states and payers have tied the introduction of guidelines to regulations that dictate, and mandate for that matter, certain practices. Physician groups and medical practices nationwide have adopted strategies that include individualized treatment plans, urine drug screens, and decision support processes with electronic health records.[59,60]

Interdisciplinary team approach

Historically, pain management was provided by physicians, but more recently an interdisciplinary approach that incorporates the knowledge and skills of a number of healthcare providers has been shown to be successful. An effective interdisciplinary team may include the following members: patient, family, physician, nurse, pharmacist, psychologist, physical therapist, occupational therapist, recreational therapist, vocational counselor, dietician, social worker, support staff, and volunteers.[61] The composition of the team will be dictated by the population of patients being treated, practice site, and resources available. As opposed to a multidisciplinary team where each team member has a specific role, an interdisciplinary team approach is one in which team members are collaborators who share in consensus-based treatment decisions and accountability. This team-based approach can be used in the acute, chronic, and cancer pain treatment facilities and in all age groups.

An interdisciplinary assessment should guide the development of a treatment plan.[61] Each team member is responsible for being familiar with the treatment plan and most importantly participating in ongoing communication. Within the team-based goals, individual team members will likely focus on aspects of the pain management. For example, physical therapists may be focusing on strength, flexibility, and endurance, whereas the pharmacist may be focusing on adverse events and signs of misuse. Although this team-based approach has been shown to be clinically cost-effective, many third-party payers are reluctant to reimburse for interdisciplinary treatment.[62-65] Ongoing advocacy efforts are focused on educating payers on the long-term benefits of this approach.

Pharmacist's role

The pharmacist can play an important role in many aspects of pain management.[61,66,67] In the retail setting, pharmacists are most often considered the gatekeeper of prescriptions. They may be the first to have proof that a patient is participating in aberrant behaviors, such as forging prescriptions or requesting refills early. It is the pharmacist's professional responsibility to notify local law enforcement agencies if there is any proof of stealing or forging prescriptions, deliberately lying to get more pain medication, or stealing or trading prescription drugs.[67] Additionally, pharmacists can query an electronic PDM program prior to dispensing an opioid prescription to identify any concerns with the patient's past opioid prescription use.

Pharmacists can play a much bigger role, however, even in the retail setting. As a trusted member of the community and trained in effective communication and assessment, pharmacists can be a patient advocate by providing effective, unbiased education about the benefits and risks of opioid therapies, available treatment alternatives, side effects, possible drug interactions, and the importance of complying with a treatment plan.[66,67] Pharmacists should also encourage patients to use one pharmacy to reduce the risk of overdose from inadvertent drug interactions or lack of understanding of full medication lists/diseases. Management of opioid side effects (e.g., constipation prevention, management of nauseas, pruritus) is also an important role of the pharmacist. Earlier articles in this continuing education pain management series appearing in the April, May, and June issues of *Drug Topics* provide a good summary of side-effect management.

Pharmacists who want to take a more active role in managing pain can inquire about whether patients have a treatment agreement with their provider and if so, request a copy. This can allow the pharmacist to play a role in accountability associated with pain agreements. With collaborative practice opportunities, a pharmacist could develop a role in assessing urine drug tests and pertinent laboratory tests as well as assessment and dose adjustment to assist in appropriately managing pain.

Conclusion

A thorough understanding of the regulatory and ethical issues associated with pain management is necessary to provide effective medication therapy management in patients with pain. Patients at high risk of opioid misuse, abuse, or addiction can be effectively treated with opioid therapy (if it is the best therapeutic option) as long as the interdisciplinary team has appropriately assessed the patient's risk and implements an individualized monitoring program. If aberrant opioid analgesic use behaviors are identified in a patient receiving opioid therapy, the interdisciplinary team, including a pharmacist, should promptly address these behaviors and modify the treatment and/or monitoring as appropriate. With this approach, opioid therapy can be successfully and safely used even in patients with the potential for or history of aberrant opioid analgesic behaviors.•

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

Pause&Ponder

If you suspect a patient may have some signs of aberrant opioid analgesic use behaviors, how would you engage the patient and the healthcare team?

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. Which of the following variables have been associated with a higher risk of misuse, abuse, and addiction when opioids are prescribed for chronic pain?
- **a.** Age >40 years
- **b.** History of drug addiction in siblings
- **c.** Occasional marijuana use
- **d.** Significant alcohol use

2. A comprehensive assessment of medical conditions, and physiologic/behavioral/genetic predisposition of candidates for opioid therapy includes:
- **a.** Physical exam and history
- **b.** Urine drug screening for opioids
- **c.** Review of prescription monitoring program (PMP) report
- **d.** Laboratory assessment

3. American Society of Addiction Medicine defines addiction as:
- **a.** An inability to consistently abstain from reward
- **b.** A primary, chronic disease of reward, motivation, memory and related circuitry
- **c.** A progressive disorder cycling between relapse and remission
- **d.** A primary, chronic disease of relapse, demotivation, memory and related circuitry

4. Which of the following might be useful information from a PMP report?
- **a.** Identification of aliases and previous addresses used by the patient
- **b.** Identification of methods of payments used for each reported medication
- **c.** Identification of prescriber information for each reported medication
- **d.** All of the above

5. To qualify for participation in PMP Information Architecture (PMIX), a state must demonstrate that:
- **a.** It has a memorandum of understanding to share with the identified exchange partner(s)
- **b.** It has legislation enabling it to share live patient data with other states
- **c.** Neither A or B
- **d.** Both A and B

6. The rationale behind urine drug monitoring in the outpatient setting is:
- **a.** To confirm that the patient is taking the prescribed medication
- **b.** To detect the presence of illicit, nonprescription medication(s)
- **c.** For workplace drug testing programs
- **d.** All of the above

7. Which of the following drugs are not on the list of 5 mandated to test for by the U.S. Department of Health and Human Services in the workplace?
- **a.** Clonazepam
- **b.** Morphine
- **c.** Marijuana
- **d.** Cocaine

8. Which of the following federally mandated levels for drug detection is correctly paired?
- **a.** Benzodiazepines = 300 ng/mL
- **b.** Cocaine = 250 ng/mL
- **c.** Opioids = 300 ng/mL
- **d.** All of the above

9. A difference between quantitative and qualitative analysis for drug detection is:
- **a.** Qualitative analysis is the gold standard
- **b.** Qualitative analysis is 99% specific and 99% sensitive
- **c.** Quantitative analysis is commonly done in-house
- **d.** Quantitative analysis can provide identification of specific compounds in the case of true-positive results

10. Pain agreements are agreements between provider and patient that generally state:
- **a.** The patient must use multiple pharmacies for all their pain medications
- **b.** The patient must accept prescriptions for pain medications from any provider
- **c.** The patient must use a single pharmacy for all their pain medications
- **d.** The patient must not agree to random urine screens

11. Which of the following monitoring recommendations is correct for a low-risk patient?
- **a.** Urine drug screening every 1-2 years; PMP review twice yearly
- **b.** Urine drug screening every 1-2 years; PMP review 3 times yearly
- **c.** Urine drug screening every 6-12 months; PMP review twice yearly
- **d.** Urine drug screening every 6-12 months; PMP review 3 times yearly

12. Monitoring for patients with "high risk" for opioid misuse or abuse should include:
- **a.** Yearly urine drug testing
- **b.** PMP 4 times a year
- **c.** Avoidance of any opioid use
- **d.** Adjusting medications to the most effective dose quickly to gain patient trust

13. The 4 "As" that should be monitored in a patient initiating opioid therapy include:
- **a.** Analgesia, activities of daily living, adverse effects, and addiction
- **b.** Analgesia, adherence, adverse effects, and aberrant behavior
- **c.** Analgesia, activities of daily living, adverse effects, and aberrant behavior
- **d.** Analgesia, adherence, adverse effects, and addiction

14. When initiating a discussion about potentially aberrant behavior, it is best to:
- **a.** Take a nonjudgmental stance
- **b.** Ask yes/no questions
- **c.** Start with identifying signs of chemical coping
- **d.** Avoid showing curiosity about situation

15. Which of the following is an example of intensified monitoring in a patient suspected of addiction development?
- **a.** Obtain a psychiatric history
- **b.** Prescribe a limited supply of opioid
- **c.** Make frequent appointments to assess pain relief only
- **d.** Limit opioid dose increases

16. Structured opioid therapy should only be used in patients who are not acquiring opioids from other sources and do not:
- **a.** Alter the route of prescribed opioids
- **b.** Use morphine
- **c.** Have regular pill counts
- **d.** Use long-acting opioids

17. Which of the following opioids should be avoided in patients treated with a structured opioid therapy?
- **a.** Buprenorphine
- **b.** Codeine
- **c.** Hydromorphone
- **d.** Morphine

18. Which of the following is true about a patient currently addicted to morphine?
- **a.** The patient should undergo addiction treatment.
- **b.** The patient should undergo structured opioid therapy.
- **c.** The patient should receive therapy with a short-acting opioid.
- **d.** The patient should receive therapy with low-abuse potential opioid.

19. An interdisciplinary team approach is one in which:
- **a.** Each team member is a collaborator who shares in consensus-based treatment decisions
- **b.** Has a specific role
- **c.** Is only effective in the outpatient setting
- **d.** Is paid for by most third-party payers.

20. Which of the following about the pharmacist's role in pain management is true?
- **a.** Pharmacists are not allowed to request a copy of a pain agreement.
- **b.** Pharmacists are not required to notify local law enforcement if proof exists of forged prescriptions.
- **c.** Pharmacists are not required to query prescription monitoring program database before dispensing a new opioid prescription.
- **d.** Pharmacists are not allowed to dispense buprenorphine.

LEGAL COMPLIANCE Ned Milenkovich, PharmD, JD

HELP Committee passes federal track and trace bill

In May 2013, the Senate's Health, Education, Labor and Pensions (HELP) Committee passed a track and trace bill known as the *Drug Supply Chain Security Act*. The bill is a result of a widespread problem—counterfeit drug products entering the U.S. supply chain over the past several years.

Regulators have been attempting to create a trusted pedigree for drugs for some time, so that a drug may be "tracked" as it passes downstream the supply chain and "traced" back to its origins, if necessary.

Senators support track and trace

Senators Michael Bennet (D-Colo.), Richard Burr (R-N.C.), Tom Harkin (D-Iowa), and Lamar Alexander (R-Tenn.) are key supporters of the bill. They believe that federal legislation would improve patient safety by replacing a current "patchwork of state product tracing laws with a strong, uniform standard that would ultimately result in electronic, interoperable unit level product tracing for the entire country."

Harkin added, "[e]nsuring the integrity and security of our prescription drug distribution system is critically important. To ensure consumers know that the medications they take are safe—not adulterated, counterfeit, or otherwise compromised, it is important to know where these drugs have been at every step of the way—from the manufacturer to the pharmacy." Notably, several previous attempts at passing federal legislation have failed due to opposition.

Details of the bill

The bill moves from a lot-level tracing system to a unit-level tracing system over the next 10 years. If passed into law, the bill would require the entire drug supply chain, including manufacturers, repackagers, wholesale distributors, third-party logistics providers, and dispensers, to exchange 1) transaction information, 2) transaction history, and 3) transaction statements, as applicable, whenever there is a change of ownership. It would also be a violation of law if any member of the supply chain accepts drugs without being provided the required transaction information. The proposal also requires FDA to maintain a database of wholesale distributors to be made available on FDA's website so that appropriately licensed wholesalers may be identified.

Other highlights of the bill include:

- Product identifiers must be affixed to a product within 4 years of the law's enactment
- Manufacturers may only distribute their products to authorized trading partners
- Within one year, manufacturers must have systems to identify counterfeit products
- National requirements must be established that pre-empt state laws
- New licensing requirements in effect for wholesalers
- FDA will publish draft guidance on track and trace requirements
- Regulators would need to request data from entities; no real-time databases
- Transaction history must be maintained for 6 years after the date of the transaction

Stakeholders provide feedback

Several stakeholders chimed in with remarks on the draft bill. Some commended the bipartisan commitment and touted that it would better protect patients and consumers by creating a single and uniform national solution to supply chain integrity concerns. The bill is being pushed for passage into law by the end of this summer. 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.*

Refresh Optive Advanced Lubricant Eye Drops is available in a preservative-free formula for sensitive eyes.

Refresh Optive Advanced Lubricant Eye Drops hydrates the eye's surface and prevents natural tears from evaporating with a lipid enhancement.

Soothe Lubricant Eye Drops-Long Lasting provides quick, long-lasting relief from dry eye syndrome.

OTC

Finding relief for your eyes and ears

MIRANDA HESTER, CONTENT COORDINATOR

When they work perfectly, most of us don't think very much about our eyes. However, dry eye syndrome can make our lives miserable. Signs and symptoms of dry eye can include burning, stinging, or a scratchy feeling in our eyes. At times, our eyes may be irritated, red, and sensitive to light. Some dry eye sufferers may have difficulty wearing their contact lenses.

When customers are on the look out for a solution to this common ailment, the following products can help provide relief.

Allergan has released **Refresh Optive Advanced Lubricant Eye Drops** to provide relief from dry eye symptoms. The artificial tear formula hydrates the eye's surface cells, lubricates the eye, and prevents natural tears from evaporating with a lipid enhancement. While customers who use the drops on a regular basis should see their eye doctor for stronger treatment options, Refresh Optive is safe to use as often as needed. Refresh Optive also comes in a preservative-free formula that offers the same benefits.

Dry eye relief is at hand with Alcon's **Systane ULTRA Lubricant Eye Drops**, also available in a preservative-free formula. The drops use polyethylene glycol and propylene glycol as lubricants to provide relief for the burning and irritation common to dry eye sufferers. ULTRA drops come in a 10-mL bottle as well as a special "Home and Away" pack that comes with a 10-mL bottle to keep at home and a 5-mL one to take on the go.

Are your customers suffering from overworked eyes and looking for relief? Bausch + Lomb's **Soothe Tired Eyes Lubricant Eye Drops** can bring relief. The formula contains glycerin, which won't cause eyes to blur, and provides quick moisture. Customers can also get long lasting relief with the **Soothe Lubricant Eye Drops – Long Lasting** formulation. For customers looking for relief from common eye irritants such as pollen, foreign material, and chlorinated water, Bausch + Lomb's **Advance Eye Relief Eye Wash** can provide relief. The Eye Wash's purified water can be used as often as needed and can be used with or without the provided sterile eye cup.

Customers looking for eye health supplements can look to **Nordic Naturals Arctic Cod Liver Oil Soft Gels, DHA,** and **Omega Vision**. The Cod Liver Oil Soft Gels contain wild

PHOTOS COURTESY OF ALLERGAN / BAUSCH + LOMB

Nordic Naturals Artic Cod Liver Oil Soft Gels, DHA, and Omega Vision are easy to swallow and formulated to prevent an aftertaste.

PHOTOS COURTESY OF NORDIC NATURALS

Arctic cod oil and is flavored with lemon to help prevent a fishy aftertaste. Three soft gels can be taken daily with food. The DHA soft gels are made with deep sea fish oil and strawberry flavored to prevent aftertaste. The soft gels are smaller than other DHA supplements, making them easier to swallow. Unflavored, the Omega Vision tablets contain omega-3s, lutein, and zeaxanthin, which can help provide relief from common eye discomfort symptoms and provide protection against ultraviolet light.

Earwax blockage

Some customers may seek relief from earwax blockage, one of the most common ear problems that physicians see. Customers with earwax blockage may complain of hearing problems, dizziness, ear pain, itching, or plugged ears.

Customers with earwax buildup can find relief with either the **ACU-Life Ear Irrigator** or the **ACU-LIFE Earwax Removal Syringe**. Both feature a tri-stream tip to direct the cleaning fluid to ear canal walls, a flared design to prevent inserting past a safe space, and an exit portal to allow for fluid draining. The Ear Irrigator also comes with 4 ounces of a saline solution.

Prestige Brand's **Debrox Earwax removal kit** uses a carbamide peroxide microfoam solution to help remove

Continued on pg. 70

Finding relief for your eyes and ears

Continued from pg. 69

earwax buildup and then a rubber bulb syringe to irrigate the foam after the application of the peroxide solution. The solution is gentle enough to use twice a day for up to 4 days.

Customers should see their doctor if their earwax buildup continues to be problematic after the fourth day. For customers who've already bought the kit or own a rubber bulb syringe, the solution is available on its own as Earwax Removal Aid.

Ear pressure regulation

Customers looking for relief from pressure changes on rollercoasters or airplane cabins can use **EarPlanes** by Cirrus Healthcare. EarPlanes are pressure-regulating ear plugs made up of two parts: a silicone ear plus and a ceramic pressure regulator. The earplug provides an airtight seal.

The pressure regulator is exposed on one end to the external air pressure and on the opposite end it's exposed to the sealed part of the air. As the pressure changes, the pressure differential changes causing the air to move in and out of the ear canal. EarPlanes are available in adult and children's sizes. DT

Customized targeted messaging builds patient loyalty

Continued from pg. 43

For example, a typical past-due refill reminder saying that your script is overdue probably doesn't have the same impact as a message from the community pharmacist whose voice is recognizable.

A million more

Every quarter, Prescribe Wellness focuses on a new preventive healthcare challenge to engage patients and encourage them to follow through with a visit to their local pharmacy. For example, Prescribe Wellness has worked to encourage patients of all ages to get their annual influenza vaccination. By segmenting the population of the pharmacies' database, pharmacists were able to send communications using social media to encourage patients to visit their local pharmacy for immunizations. They also have targeted patients to drive them to the website, *amillionmore.com*, powered by Prescribe Wellness. This educational website also includes a search feature to locate an independent pharmacy nearby.

Last quarter, during the flu shot campaign, Prescribe Wellness tailored messages for younger adults to try to raise awareness about the importance of flu vaccinations. "The underlying message is that you may not be the one who gets sick and hospitalized, but do this for your family and for your community," Babbington said.

Prescribe Wellness has partnered with pharmacy associations to encourage immunizations for flu prevention. They include the Arizona Pharmacy Association, California Pharmacists Association, North Carolina Association of Pharmacists, Pharmacists Society of the State of New York, Pennsylvania Pharmacists Association, Georgia Pharmacy Association, Iowa Pharmacy Association, and Oklahoma Pharmacists Association. These associations enrolled hundreds of pharmacies last year, with a goal of including 1,000 pharmacies before the peak of the flu season.

Pharmacists who have worked with Prescribe Wellness have described the customized, targeted messaging as successful based on anecdotal evidence, Babbington said.

"Although many independent pharmacists have their own websites and use them for promotion, our package includes a single platform that can deliver voice, text, and social media pushes on behalf of independent pharmacists," he said. "We also provide services where they have a whole kit to reach out to local media, sample letters that they can do for various faith-based organizations, schools, and civic groups." DT

Advertiser Index

Generics Supplement Advertiser Index

*Indicates a demographic advertisement.

RX & OTC

New products

PHOTOS COURTESY OF GLAXOSMITHKLINE

RX CARE

New drugs

FDA has approved two new cancer drugs, both from GlaxoSmithKline. **Tafinlar** (dabrafenib) **[1]** and **Mekinist** (trametinib) **[2]** are approved for oral use as single agents — not in combination — against melanoma, the deadliest form of skin cancer. Tafinlar was approved to treat patients with melanoma whose tumors express the BRAF V600E gene mutation, while Mekinist is for patients with either the BRAF V600E or V600K gene mutations. About half of skin melanomas have a BRAF mutation. FDA also approved the THxID BRAF test, made by France's bioMérieux, which will be used to determine whether a patient's melanoma cells have the V600E or V600K mutation in the BRAF gene. Advanced melanoma patients who received Tafinlar had a delay in cancer growth that was 2.4 months longer than patients treated with a standard chemotherapy drug, dacarbazine. Subjects with the BRAF V600E or V600K gene mutation who received Mekinist had a delay in cancer growth that was 3.3 months longer than that seen in subjects given standard chemotherapy. **(www.tafinlar.com / us.gsk.com)**

Eisai has announced that **Belviq** (lorcaserin HCl) CIV tablets **[3]**, the first prescription treatment option for chronic weight management approved by the FDA in over a decade, is now available in most U.S. pharmacies. Approved by FDA in June 2012, the product may help some obese adults or overweight adults who also have weight-related medical problems lose weight and keep the weight off. It should be used with a reduced-calorie diet and increased physical activity. **(www.belviq.com)**

FDA has approved and granted orphan product designation to Raptor Pharmaceuticals' **Procysbi** (cysteamine bitartrate) delayed-release capsules for the management in children and adults of nephropathic cystinosis, the most severe of three types of cystinosis, a rare genetic condition that affects an estimated 500 patients in the United States and about 3,000 patients worldwide. Cystinosis causes cysteine, a protein building block, to build up in every cell of the body. The cysteine buildup causes kidney problems and may lead to slow body growth and small stature, weak bones, and developing and worsening kidney failure. If not treated in early childhood, cystinosis can be fatal. FDA-approved drugs used to treat cystinosis include Cystagon (cysteamine bitartrate), an immediate-release tablet that was approved in 1994, and Cystaran (cysteamine ophthalmic solution) eye drops, from Sigma Tau Pharmaceuticals, approved to treat corneal cystine crystal accumulation and launched in May. Procysbi is intended for patients ages 6 years and older. While Cystagon is taken every six hours around the clock to control cystine levels, Procysbi is a long-acting formulation that is taken every 12 hours. **(www.procysbi.com)**

FDA recently approved Cangene's **Botulism Antitoxin Heptavalent (A, B, C, D, E, F, G)-(Equine)** to treat patients showing signs of botulism following documented or suspected exposure to botulinum neurotoxin. This heptavalent antitoxin is the only product available for the treatment of botulism in adults, and for cases of infant botulism caused by nerve toxins other than types A and B. The product, which will be stored in the Strategic National Stockpile for emergency preparedness and responses and distributed through the CDC's Drug Service, is derived from horse plasma and contains a mixture of antibody fragments that neutralize all of the seven botulinum nerve toxin serotypes known to cause botulism. Botulism is a rare but serious paralytic illness caused by a nerve toxin produced by the bacterium *Clostridium botulinum* and sometimes by strains of *Clostridium butyricum* and *Clostridium baratii*. In the United States, an average of 145 cases are reported each year, and of these, approximately 15% are foodborne, 65% are infant botulism, and 20% are wound-related. In foodborne botulism, symptoms generally begin 18 to 36 hours after eating a contaminated food, but they can occur as early as 6 hours or as late as 10 days. **(www.cangene.com)**

Liptruzet, a cholesterol-lowering drug that combines ezetimibe with atorvastatin, has been approved by FDA. According to Merck, Liptruzet tablets are for the treatment of high LDL (low-density lipoprotein) cholesterol in patients with primary or mixed hyperlipidemia alongside a special diet when diet alone is not enough. Hyperlipidemia is an excessively high concentration of fats (lipids) in the blood. Merck says this product treats two sources of cholesterol; with atorvastatin, it reduces the production of cholesterol in the liver; with ezetimibe, it inhibits the absorption of cholesterol in the digestive tract. The dosage range of Liptruzet is 10/10 mg/day to 10/80 mg/day. The product has not been shown to lower the risk of cardiovascular disease, including stroke and heart attack. **(www.liptruzet.com)**

New indications

In May, Janssen Biotech's **Simponi** (golimumab) was approved as a new therapeutic option for patients living with moderately to severely active ulcerative colitis (UC), who have demonstrated corticosteroid dependence or who have had an inadequate response to or failed to tolerate oral aminosalicylates, oral corticosteroids, azathioprine, or 6-mercaptopurine. The product is the first and only subcutaneous biologic treatment approved to induce and maintain clinical response and improve endoscopic appearance of the intestinal lining. Simponi is indicated to induce clinical remission and achieve and sustain clinical remission in induction responders.

As many as 700,000 people in the United States are affected by UC, a chronic inflammatory bowel disease marked by inflammation and ulceration of the innermost lining of the colon. To treat UC, the Simponi dose regimen consists of 200 mg subcutaneously injected at week 0, followed by 100 mg at week 2, and then 100 mg every 4 weeks, thereafter. **(www.simponi.com)**

FDA has approved Genentech's **Tarceva** (erlotinib) tablets, used in initial treatment of metastatic non-small-cell lung cancer (NSCLC). The approval was based on the results of the Phase 3 study, named EURTAC, which evaluated the first-line use of Tarceva versus platinum-based chemotherapy in people with EGFR-activating mutation-positive advanced NSCLC. According to Genentech, 10% to 30% of people worldwide with lung cancer have tumors that test positive for certain EGFR mutations. FDA has also approved the cobas EGFR Mutation Test, which was developed by Roche and validated in the EURTAC study. Tarceva is already approved in the United States, irrespective of histology or biomarker status, for people with advanced-stage NSCLC whose cancer has not spread or grown after initial treatment with certain types of chemotherapy. **(www.tarceva.com)**

New generics

Late in May, FDA approved **trospium chloride ER**, a generic drug for incontinence made by Perrigo Co. The 60-mg extended-release capsules are a once-daily treatment for overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency. The drug is a generic version of Allergan's Sanctura XR. Trospium chloride antagonizes the effect of acetylcholine on muscarinic receptors in cholinergically innervated organs including the bladder. Its parasympatholytic action reduces the tonus of smooth muscle in the bladder. The product is now shipping. **(www.perrigo.com)**

New OTC

Nordic Naturals has launched **ProEPA Elite**, **[4]** featuring a high dose (1,600 mg per serving) of omega-3 eicosapentaenoic acid (EPA), an essential fatty acid that has anti-inflammatory properties and supports heart health. ProEPA Elite is an EPA-only formula that contains a dose of fish oil similar to a much-studied ethyl-ester EPA formulation. This dose of EPA has been demonstrated in clinical studies to be beneficial in reducing triglycerides and other cardiovascular risk factors. ProEPA Elite differs from the study product in that it is formulated in the more bioavailable triglyceride form that is available over the counter. Nordic Naturals offers four products in varying amounts of omega-3 EPA: ProEPA, ProEPA Xtra, ProEPA Elite, and ProEPA with Concentrated GLA. **(www.nordicnaturals.com)** DT

PHOTOS COURTESY OF EISAI / NORDIC NATURALS

Products & Services

Brokers

SEE MORE BROKERS ON NEXT PAGE!

Products & Services

Brokers

Consulting Services

Products & Services

Continuing Education

Financing

Education

JP AT LARGE Jim Plagakis, RPh

Pharmacognosy is an elective worth pursuing

Pharmacognosy is no longer a required course in pharmacy education, although some schools offer it as an elective. The newer schools do not offer it at all. Do new student pharmacists even know the definition of the word?

After brunch in a coffee shop in Sarasota, Fla., I wandered next door to the Kiev Delicatessen. At the end of the deli counter, I found a huge display of herbal teas, poultices, papers, capsules, suppositories, creams, and lotions.

They were exhibited in an area that was not self-serve, probably 500 different products with Russian labels. I doubted if many of these products could be purchased from American sources and sold in American pharmacies.

I dared to go behind the counter and snapped some pictures, and then I was busted by the owner.

"Why you take picture?"

"I am interested," I said. I held up my phone and pointed at the well-tended display. "I am a pharmacist. I studied pharmacognosy [drugs from plant and animal origin] for a whole year."

I had no idea what the Cyrillic words were. I picked up a brightly colored box. The source name was in English: *Nepeta cataria,* catnip. "This has been a digestive aid for decades," I said. "Unfortunately, kids smoke it to get high."

"Why you take pictures?"

I took another box. *Pausinystalia yohimbe.* "Helps a man be a man."

Yocon is a prescription-only brand name of yohimbine hydrochloride 5.4 mg. I dispensed Yocon 30 years ago for its aphrodisiac qualities. I recently read that *yohimbine* helps with post-traumatic stress disorder. There are plenty of OTC yohimbine products hawked on the Internet, but this is a serious drug. I do not believe they synthesize it. The bark of the plant is the only source.

"Delete pictures."

I complied, bought some tea cookies from Macedonia, and left the deli with a fresh batch of questions. Something has happened to the art and science of pharmacy, and it has everything to do with greed and gluttony and the quest for more profits.

Any more breakthrough drugs?

I think that I can say with confidence that the search for new therapeutic drugs is in the laboratories of Big Pharma. Computers process countless molecules through algorithms that speculate where the next entirely new class of affordable drugs will be found. This apparently is the cost-effective path to profitable new products. The problem is that it hasn't worked lately. Have you noticed that there have been no really new drugs for over a decade or more, unless you count the specialty drugs you see on television, which cost $5,000 a month?

Tweaking drugs for new indications is cheaper than sending someone into the Amazon to find new cures. Nature's laboratory will never run out of really good drugs. That is Pharmacognosy. Although no longer a required course in pharmacy education, some schools offer it as an elective. The newer schools do not offer it at all. Do new pharmacists even know the definition of the word?

Don't try to tell me that it was a Cowlitz Indian shaman who showed up at Squibb in 1967 shaking a hunk of Pacific yew tree (*Taxus brevifolia*), "Big magic cure cancer in bark." Monroe Wall and Mansukh Wani are credited with isolating Taxol from the yew bark. I doubt if Monroe or Wani ever muddied their boots in the verdant old growth temperate rainforest below Mount St. Helens. It had to be a pharmacognocist who struggled through the thick vegetation, don't you think? Who gave him the hint where to look? Perhaps it really was the Indian shaman who passed on the legend that spawned a billion-dollar drug class. Taxanes have saved millions of lives. These drugs are still processed from plant origin.

Contemporary pharmacy students come out of school these days being able to race the clock, but do they have a hint that galantamine (Razadyne) comes from the genus *Narcissus* (daffodil)?

I know it is the leaden feet of the ACPE that need to be held to the fire. What was ACPE thinking allowing such a vast universe of pharmacy to be simply washed away, and for whose benefit? New pharmacists deserve better. 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.*

NEW CE SERIES

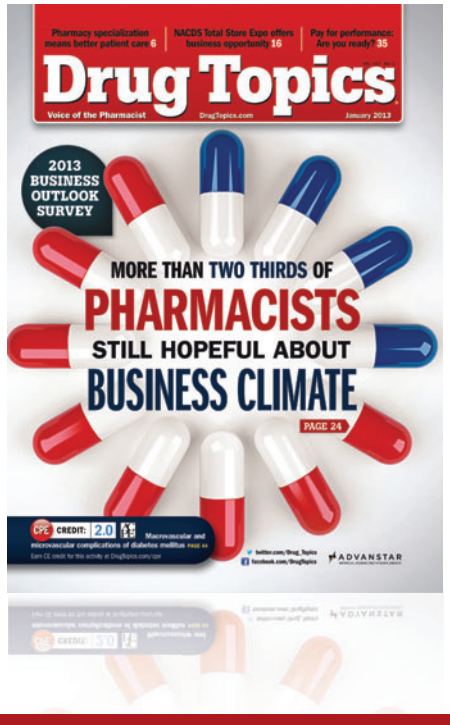
The *Ideal* Partnership

Putting Knowledge into Action

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

FREE! 12-Credit CE Course

Pain Management Considerations in Medication Therapy Management



Comprehensive Pain Management Training

- **Earn 10 hours of CPE credit with Pain Management knowledge-based activities through *Drug Topics*.**
  (April 2013-August 2013)
- **Earn 2 hours of CPE credit with Pain Management application-based activities through online interactive case studies.**
  (September 2013-October 2013)

Complete 1 activity or as many as you need!

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

NOW AVAILABLE from **MYLAN**®

2013GBR®
Generic Brand Reference

How do we demonstrate our commitment to pharmacy professionals every day?

See inside.

We provide educational resources, like the *GBR*®—*Generic Brand Reference*—Guide, to pharmacists and pharmacy technicians. The 2013 *GBR* Guide, which contains a comprehensive, cross-referenced listing of generic and brand pharmaceuticals, is now available in print and as an app for Apple®* devices. In mid-2013, it will also be available for Android™† and BlackBerry®‡ smartphones.

To order the FREE print edition, go to Mylanpharms.com. To download the FREE app, scan the code at right for Apple devices, or go to the appropriate app store, search for "Mylan *GBR* Guide," and follow the instructions.

Discover how Mylan supports you with high quality medicine and resources.

Mylanpharms.com

**Registered trademark of Apple, Inc.*
†Trademark of Google Inc.
‡Registered trademark of Research in Motion (RIM).

Mylan®
Seeing is believing